MENINGIOMAS AND HORMONAL RECEPTORS-AN IMMUNOHISTOCHEMICAL STUDY

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M.D. DEGREE

In

PATHOLOGY – BRANCH III

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APRIL 2015

DECLARATION

I hereby declare that the dissertation entitled **"MENINGIOMAS AND HORMONAL RECEPTORS"** is a bonafide research work done by me in the Department of Pathology, Coimbatore Medical College during the period from July 2013 to July 2014 under the guidance and supervision of **Dr.C.LALITHA, M.D**., Head of department & Professor, Department of Pathology, Coimbatore Medical College.

This dissertation is submitted to The Tamilnadu Dr.MGR Medical University, Chennai towards the partial fulfilment of the requirement for the award of M.D., Degree (Branch III) in Pathology. I have not submitted this dissertation on any previous occasion to any University for the award of any Degree.

Place: Coimbatore

Date: Dr.S.SUPASAKTHI

CERTIFICATE

This is to certify that the dissertation entitled "**MENINGIOMAS AND HORMONAL RECEPTORS-AN IMMUNOHISTOCHEMICAL STUDY ”** is a record of bonafide work done by **Dr.S.SUPASAKTHI** in the Department of Pathology, Coimbatore Medical College, Coimbatore under the guidance and supervision of **Dr.C.LALITHA**., **M.D**., Professor, Department of Pathology, Coimbatore Medical College and submitted in partial fulfilment of the requirements for the award of M.D. Degree (Branch III) in Pathology by The Tamilnadu Dr. MGR Medical University, Chennai.

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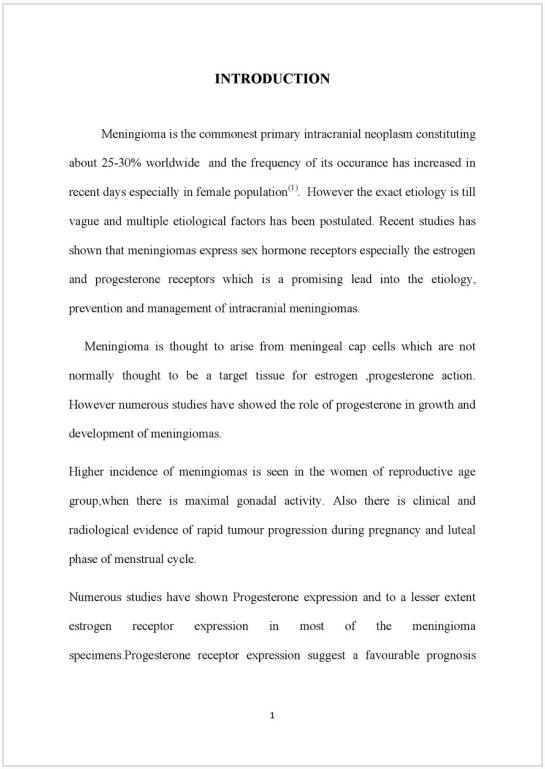

INTRODUCTION

Meningioma is the commonest primary intracranial neoplasm constituting about 25-30% worldwide and the frequency of its occurance has increased in recent days especially in female population[1]. However the exact etiology is till vague and multiple etiological factors has been postulated. Recent studies has shown that meningiomas express sex hormone receptors especially the estrogen and progesterone receptors which is a promising lead into the etiology, prevention and management of intracranial meningiomas.

Meningioma is thought to arise from meningeal cap cells which are not normally thought to be a target tissue for estrogen ,progesterone action. However numerous studies have showed the role of progesterone in growth and development of meningiomas.

Higher incidence of meningiomas is seen in the women of reproductive age group,when there is maximal gonadal activity. Also there is clinical and radiological evidence of rapid tumour progression during pregnancy and luteal phase of menstrual cycle.

Numerous studies have shown Progesterone expression and to a lesser extent estrogen receptor expression in most of the meningioma specimens.Progesterone receptor expression suggest a favourable prognosis

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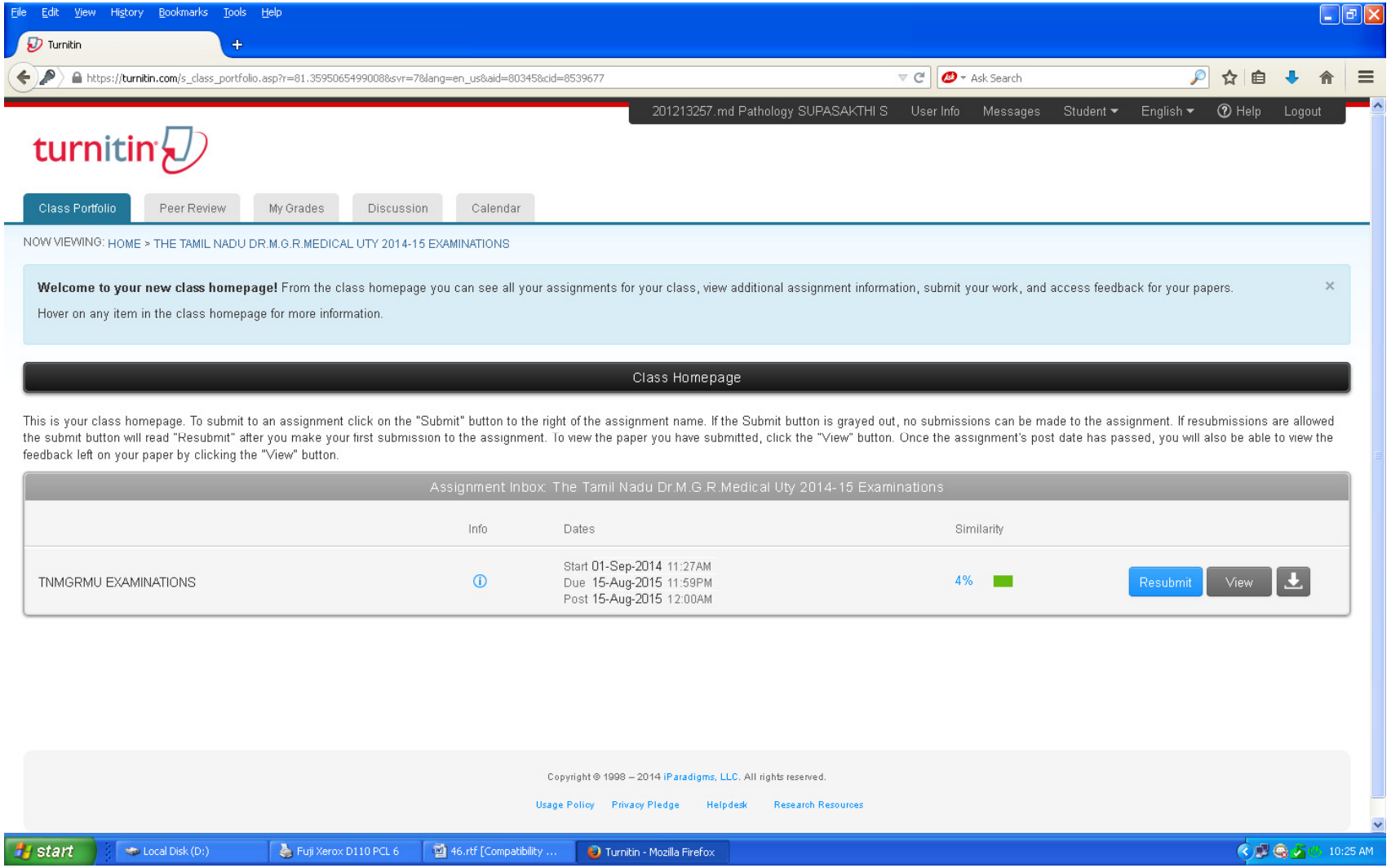
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ABSTRACT

BACKGROUND:

Meningiomas constitute about 13-26% of primary intracranial tumours. Although most of the meningiomas are benign grade I tumours,they show a recurrence rate of about 30% . Detection of this morphologically benign and biologically aggressive meningiomas cannot be made by routine histology alone. Thus in the present study Progesterone receptor, Estrogen receptor and Ki67 markers were used as an adjuvant approach in the identification of these biologically aggressive meningiomas.

OBJECTIVE:

To assess the Estrogen receptor ,progesterone receptor and Ki67 expression and to compare and to correlate them demographically, histologically and immunohistochemically.

MATERIAL AND METHODS:

This is a cross sectional study conducted for a period of one year (July 2013-july 2014) in the Department of Pathology,Coimbatore Medical College ,Coimbatore. Thirty cases of meningioma were asssesed immunohistochemically and correlated with various clinico –pathological parameters.

RESULTS:

Thirty cases of meningioma were included in the study all of which were grade I tumours. Mean age of all cases were 45 .7 +/- 13.1 years. Females outnumbered males with F: M ratio of 2.7:1. Progesterone receptor positivity seen in about 19 out of 30 cases(63.3%), with none of the cases showing estrogen receptor immunoreactivity. Also PR immunoreactivity was higher in females(68%). Age,location of tumor and subtypes has no correlation with PR.Recurrence was noted in 7 out of 30 cases .The recurrence rate was found to be higher in males(25%). Progesterone expression was higher in Non recurrent tumours (78%). In recurrent tumours, PR expression was decreased(14%) but in contrast Ki67 expression was 100% . There is an inverse relationship between Ki67 and Progesterone receptor expression. Age, Location of tumour and the meningioma subtypes had no role in predicting the recurrence.

CONCLUSION:

Although meningiomas express progesterone receptor, it is independant of Estrogen receptor, unlike the other hormone dependant tumours like breast and uterus[58].Expression of Progesterone receptor is associated with lesser recurrence and better prognosis.. Progesterone receptor can be used along with other histological parameters for prognostication of meningiomas[59,60]

Thus , in the grading of meningiomas ,histopathological examination alone is not sufficient, ancillary tests with Progesterone receptor and proliferative marker should be included for prognostication of meningiomas.

Key words: Meningioma, Progesterone receptor,Ki67 , immunohistochemical study.

INTRODUCTION

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Meningioma is the commonest primary intracranial neoplasm constituting about 25-30% worldwide and the frequency of its occurance has increased in recent days especially in female population[(1)]. However the exact etiology is till vague and multiple etiological factors has been postulated. Recent studies has shown that meningiomas express sex hormone receptors especially the Estrogen and Progesterone receptors which is a promising lead into the etiology, prevention and management of intracranial meningiomas.

Meningioma is thought to arise from meningeal cap cells which are not normally thought to be a target tissue for estrogen ,progesterone action. However numerous studies have showed the role of progesterone in growth and development of meningiomas.

Higher incidence of meningiomas is seen in the women of reproductive age group, when there is maximal gonadal activity. Also there is clinical and radiological evidence of rapid tumour progression during pregnancy and luteal phase of menstrual cycle.

Numerous studies have shown Progesterone expression and to a lesser extent estrogen receptor expression in most of the meningioma specimens. Predicting the behaviour of meningiomas with routine

histopathological examination alone is not sufficient. Various literature have shown that the expression of progesterone receptor is associated with lesser recurrence and better prognosis of patients. Thus the study is aimed at assessing the expression of hormonal receptors (ER, PR) along with proliferation index in the meningiomas specimens and to correlate them histomorphologically.

AIMS AND OBJECTIVES

AIMS & OBJECTIVES

1. To analyse and compare the Estrogen receptor, progesterone receptor and Ki67 expression using immunohistochemical method.
2. To assess the histological grades and subtypes of meningiomas using Hematoxylin and Eosin sections.
3. To correlate ER, PR and Ki67 expression with histological grades and subtypes
4. To correlate ER, PR and Ki67 expression in non recurrent and recurrent tumours.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

HISTORY AND NOMENCLATURE:

The earliest evidence of meningioma was found in a 365,000years old skull, in Germany .An autopsy done by Felixplater of the University of Basel was the first literature evidence of meningioma was in 1600. The characteristic fungal like growth of meningioma was described in detail by Louis in 1774.The first successful removal of meningioma dates back to 16 century.

Until early twentieth century these tumours were referred by various names which include Endotheliomas, Psammomas, Meningioexoepitheliomas and Arachanoid fibroblastomas.The term "meningioma" was coined by HARVEY CUSHING in 1922 for a set of tumours that occurred throughout neuraxis [(2)]. In 1938 Drs.Harvey cushing and Louise were the first to publish a monograph 313 meningiomas.Later in 1970 Charles Oberling subtyped meningiomas based on the cell structure. Another major monograph was published by John kepes after observing some 1300 cases. In 1979 World health organization(WHO) classified meningioma into seven subtypes then it was upgraded in 2000 into nine variants belonging to grade 1 ,three variants belonging each to grade 2 and grade 3.

ANATOMY AND HISTOLOGY:

The brain and spinal cord is covered by the meninges which is a tripartite coverings consisting of outer dura, middle arachanoid, inner pia mater.

The normal dura mater is a tough ,thick membrane hence it was previously referred to as "Pachymenix" which means "Thick meninges".The literal meaning of the word Dura mater is "Tough mother".It consists of two layers,the outer layer is affixed to overlying periosteum and the inner layer covers the brain matter.In the spinal region the dura mater is not attached to the spine creating extradural space.Histologically dura is a dense collagenous structure with cells having a fibroblastic appearance.Most of the meningiomas are attached to the overlying dura.[3]

Arachanoid cap cells:

The middle arachanoid layer is a "spider like" membrane.Histologically it consists of 2 types of cells.The outer cells are spindle shaped as seen in fibrous meningiomas and the inner cells are polygonal in shape.Interspersed among these are the meningothelial cell nests which are round to oval cells with slightly oval nucleus showing

delicate chromatin and inconspicuous nuclei. These aggregate into grossly visible mass “arachanoid granulations”.

The arachanoid granulations are clustered at locations where dural venous drainage is prominent that is along superior saggital sinus,major venous sinuses at skull base. These sites closely mimics meningioma distribution providing a clue that meningioma arises from arachanoid cap cells. These cells can also be found in variety of unusual locations like orbital,head and neck region and in the intraventricular region.This unusual location may be due to embryological misadventures.

Functions of Arachanoid cap cells:

a)Wraping around each other , the surface of CNS,proximal portions of CNS,blood CSF barriers.

b)Helps to maintain CSF homeostasis by protein seretion

c)Providing trophic support for migrating neuroglial cells

d)Macrophage like function rarely.

Pia mater is the inner most and inconscpicous cell layer of meninges with tight attachment to the brain matter.It follows the contour of the brain and divides into Virchow-robins spaces. Disruption of the pia- glial barrier is histologically ominous sign when evaluating meningiomas.

EPIDEMIOLOGY:

Meningiomas are the commonest intracranial neoplasm constituting about 25-30% of central nervous system neoplasms worldwide. Annual incidence rate is about six to thirteen percent per 100,000 persons. At autopsy meningiomas is an incidental finding in about 1.4% cases.Sporadic meningiomas constitute around 10% of cases.According to current studies it has been shown that atypical constitute around 20 %. Those cases belonging to malignant/anaplastic meningiomas constitute only upto 2 .2 %. The increased incidence of meningiomas is attributed to the increased diagnostic modalities and also probably the increased exogenous risk factors.

SITE PREDILECTION:

Meningiomas are typical for their location, being attached to inner surface of the duramater of meningiomas which possibly excludes other intracranial neoplasms. Majority of meningiomas arise within intracranial and intraverterbral cavities.(4)

1)Parasaggital/falx cerebri

2)cerebral convexities.

Among the intracranial tumours 40% arise over cerebral convexities closely attached to falx cerebri..Majority of the parasaggital

meningiomas occur in the middle one third. Falcine tumours may occur bilaterally with mirror image lesions on either side Other common sites include

3)sphenoid ridge

4)suprasellar

5) olfactory grooves

6)posterior fossa

7)middle fossa

8)Tentoril

9)Petrous ridges

Optic nerve sheath involvement is rare in meningiomas. Intra ventricular meningiomas arise from the rest of meningothelial tissue that is carried along with choroid plexus during embryogenesis.It occur most commonly in the lateral ventricles,more frequently left lateral ventricle than the right lateral ventricle ,the reason for which is not known.also intraventricular meningiomas are more common in children.

Spinal meningiomas tend to be more common in the thoracic region occupying the anterior and more lateral location of spine.

Multiplicity of spinal meningiomas is rare but can occur in neurofibromatosis 2 patients.

Atypical or malignant variants are more common on the lateral convexities and falx cerebri. Metastatic deposits of malignant meningioma occur in the lung,lymph node,liver,bones,pleura.

AGE & SEX PREDILECTION:

The incidence of meningiomas are more common in middle aged and elderly patients.Incidence increases with age with a median age of 64 years at the time of diagnosis. The incidence of meningiomas are less in children ie only 1.9% of all intracranial neoplasms in children are meningiomas. After the age of 35 meningiomas are the most common intracranial tumour. Meningioma occurring in hereditary syndromes like Neurofibromatosis type 2 typically occur in younger patients. The age standardized incidence rate of meningioma was 5.5per one lakh for females and 1.6 per one lakh for males.(Finnish cancer registry 2001)

Of the all intracranial neoplasms 38% in females and 20% in males are meningiomas with female to male ratio 2:1.[(5)]. In women the most common spinal tumour is meningioma. The female to male ratio in spinal meningiomas is 3-4: 1.However higher grade of meningiomas (atypical and anaplastic)are more common in male.Also childhood meningiomas

tend to be more common in males.Meningiomas in hereditary syndromes occurs equally in male and female.[6]

According to The Central Brain Tumour Registry of the United States 2011 statistical report the women to men sex ratio was 2.2:1. The actual incidence rates of meningiomas is higher than the above studies since surgical treatment and diagnosis are not done for all cases of meningiomas.[7] This is favoured by an Autopsy study by Krampla et al., 2004 which showed an prevalence of 2.8% of subclinical meningiomas in females.[8]

Risk factors :

There are multiple risk factors that have been postulated to increase the incidence of meningiomas. These are described below

1. Radiation exposure: Many studies has shown an increased risk of meningiomas following radiation exposure.These cases are associated with multifocality and aggressiveness.

   Average interval of time for tumour development following low,medium and high dose radiation is 35 years,25-27 years,19-23 years.

   Meningiomas tend to occur following low dose irradiation which constitute 800 rads for treating tinea capitis.

High dose of radiation which is 2000rads for treating primary central nervous system tumours results in multifocal.more aggressive,atypical,anaplastic meningiomas.

Radiation induced meningeal tumours tend to occur in younger age with high proliferative index.

In a study in Israel by Ron et al., 1988 the relative risk of developing meningiomas was increased in a age matched cohort study of 10,834 children treated with low dose radiation therapy for Tinea Capitis compared to a control group who didn't undergo irradiation.[9]

In a study by Al-Mefty et al., 2004 the incidence of secondary meningiomas is increased following high dose radiation therapy to the head and neck region in children for other tumours. [10]

In a study conducted by Gallowy et al., 2011 the children who had radiation treatment need long term follow up since the risk of incidence of meningiomas increases after ten years of radiation treatment. [11] A study by Strojan et al 2000,The radiation induced meningiomas occur at an younger age, are often multiple, more often anaplastic and have high tendency for recurrence.[12]

2. Occupational risk factors: The risk of meningioma is increased among men exposed to lead. Navas-Acien et al showed in his study that,Women who have occupational exposure to herbicides have

increased risk of meningiomas compared to women who were not exposed. [13]

3. Medical risk factors: Women with a previous breast cancer have an increased risk of meningioma occurance in later life compared to women without previous breast cancer.

   Custer et al., 2002 noticed increased risk for breast cancer in female meningioma patients. Uterine fibroids and endometriosis which are sex hormone related conditions are more common in females with meningiomas than controls.[14]

4. Genetic risk factors: Meningioma occurs in 50% of patients with Neurofibromatosis 2 which is an Autosomal dominant disorder. [15]

   In Neurofibromatosis 2 patients the meningiomas occur at younger age, are often multiple compared to sporadic meningiomas which occur at older age and rarely multiple. The meningiomas occurring in NF 2 patients are more often Fibroblastic subtype and also more aggressive than sporadic meningiomas. The risk of meningiomas is higher in persons with a family history of meningioma.

5. Hormonal therapy: In 2003 Jhawar et al found an increased risk of meningiomas in women who were receiving Menopausal Hormonal Therapy for the first time which increased the attention to the role of sex hormones in meningiomas.[16]

Similarly two other studies by Wigertz et al. in 2006 and Blitsteyn et al., in 2008 confirmed the above findings which provided a new angle into the incidence of meningiomas.[17],[18].

A study called The Million Women Study, a prospective which included 11,47,894 post menopausal women with a mean follow up of 5.3 years a total of 311 meningiomas were observed. This study showed increased relative risk of meningiomas of 1.34 among current users and 1.29 among past users. Among the current users the relative risk was increased to 1.44 for those who were using estrogen Only Therapy. Results on studies correlating meningioma incidence with Oral Contraceptives were inconclusive.

6. Head Injury: According to Barnett et al 1986 the chronic inflammation and granuloma formation following head injury may cause irritation of nearby meninges which leads to formation of tumour. But the association of meningioma post head injury is inconclusive according to many studies.[19]

CLINICAL FEATURES:

Symptoms and signs depends on primary location of tumour. These slow growing tumours usually produce symptoms by compressing the adjacent structures.they may grow to a considerable extent before producing clinical symptoms.This is usually seen with Olfactory groove

meningiomas.These lesions produce central scotoma,ipsilateral optic atrophy,Ipsilateral insomnia,with contralateral pappiloedema. Tumours located on the upper falx presents motor and sensory disturbances of lower extremity.More laterally located lesions produce hand and neck signs and symptoms.Base of skull tumours produce a more non-localising symptom like headache,but sometimes they may entrap the cranial nerve and produce the symptoms. Sphenoid ridge meningiomas present with unilateral visual loss with painless exophthalmos. Tuberculum sellae masses present with bilateral hemianopsia,and optic atrophy. Cerebellopontine angle meningioma present with hearing loss and cerebellar signs. Foramen magnum tumours present with spastic paresis and sensory loss of upper extremity.Underlying tumoral edema can by itself provokr neurological signs and symptoms.Rarely they may invade into overlying skull and scalp producing scalp nodules.

- New neurological deficit
- Seizure
- Symptoms of raised intracranial pressure
- Proptosis
- Cavernous sinus syndrome

DIAGNOSIS OF MENINGIOMA:

Magnetic Resonance Imaging (MRI) is the investigation of choice for the diagnosis of meningiomas eventhough Computerised Tomography (CT) can also be used and readily available. In some cases of meningiomas with adjacent bony involvement and calcifications CT is more useful than MRI.

On imaging meningiomas are seen as extra-axial masses which are round or elongated which often shows dural attachment. Meningiomas more commonly show homogenous enhancement after administration of contrast material and sometimes can show heterogenous enhancement.

On Magnetic resonance imaging ,meningiomas appear as isodense, dural based contrast enhancing masses.calcification is seen best on Computed tomography.charecteristic feature is the “dural tail” which are either dural extension of tumour or a rim of fibrovascular(reactive) tissue. Peritumoral edema is seen prominently in atypical or anaplastic meningioma.

Zee et al in his study showed that,2-10% of meningiomas show cystic in nature and may cause difficulty in diagnosis. [(20)] 24% of pediatric meningiomas show cysts which is less common in adult

meningiomas.[21] Hyperostosis of skull adjacent to meningioma seen in MRI represents direct invasion of meningioma into the skull bone.

There is no specific feature on imaging studies in routine CT & MRI which differentiates benign meningiomas from malignant meningiomas. Aggressive histological features in meningiomas can be predicted using Diffussion and Perfusion MRI.

According to Nagar et al., 2008 more aggressive tumours are associated with less water diffusivity shown in diffusion MRI and are more prone for recurrence. The vascular supply of meningiomas can be seen in perfusion MRI. It is said that the vascular supply of meningiomas differs between benign and malignant meningiomas i.e., the main blood supply of benign meningiomas is via the dural branches of external carotid artery wheras high grade meningiomas receive blood supply mainly from the Pial-Cortical branches. Hence in benign meningiomas which receives blood supply from the dural branches lack blood brain barrier and Gadolinium can permeate into the tumour tissue and shows typical curve whereas in high grade meningiomas which receives blood supply from the pial branches have blood brain barrier shows return of intensity to baseline levels on perfusion scans.

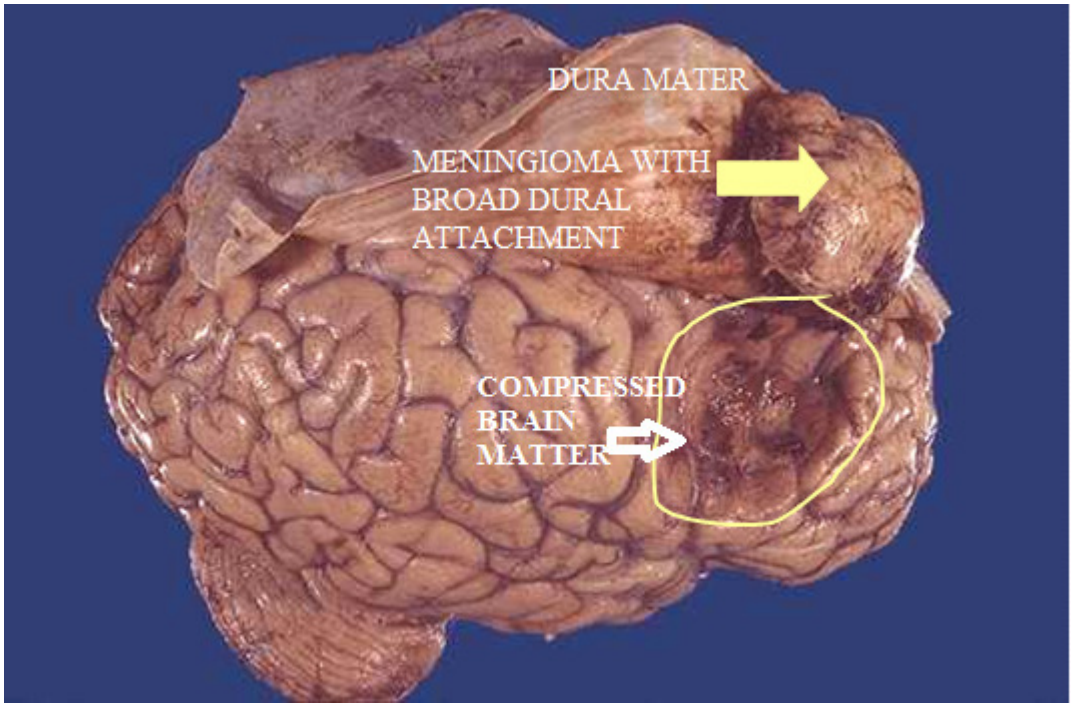
NATURAL HISTORY OF MENINGIOMAS:

Many cases of meningiomas are diagnosed incidentally due to the widespread use of CT and MRI's. This may also be the reason for increase in incidence of meningiomas of late. Majority of patients with meningiomas which was diagnosed incidentally are asymptomatic. Most of these cases show only minimal growth and can be followed up with serial imaging with treatment to be initiated if there is progress of growth.

A study by Nakamura et al., 2003, Patients less than 60 years of age seem to have increased growth potential compared to patients older than 60 years.The initial tumour size at the time of diagnosis is not a predictive factor for growth of meningioma. In meningiomas showing calcification in tumour tissue is associated with lack of growth.[22]

A study by Yano et al., 2006 showed that approximately about 1/3rd of meningiomas progress based on the natural history of these tumours. Meningiomas have potential to progress to higher grades i.e., benign to atypical or malignant.[23] Approximately 1/3rd of recurrent meningiomas are transformed to higher grade.[10]

GROSS:



Most of the meningiomas are well demarcated masses with a broad based dural attachment. They are gray white to tan, rubbery to firm consistency with a trabeculated or whorled cut surface similar to leiomyoma.sometimes they have a gritty aparance due to large number of psammoma bodies.Adjacent parenchyma is compressed. meningiomas along sphenoid wing grow as flat,carpet like masses termed “en plaque” variant. Invasion of the dura or dural sinuses is common. skull invasion gives rise to characteristic hyperostosis.They may invade the infiltrate the overlying skin with orbital extension.atypical and anaplastic meningiomas are larger with areas of necrosis.

CLASSIFICATION OF MENINGEAL TUMOURS:

According to WHO(2007) the following tumours are included in meningeal tumours[24]

- Mesenchymal non-meningothelial tumours
    a) Lipoma 8850/0
    b) Liposarcoma 8850/3
    c) Angiolipoma 8861/0
    d) Hibernoma 8880/0
    e) Solitary fibrous tumour 8815/0
    f) Fibrosarcoma 8810/3
    g) Malignant fibrous histiocytoma (MFH) 8830/3
    h) Leiomyoma 8890/0
    i) Leiomyosarcoma 8890/3
    j) Rhabdomyoma 8900/0
    k) Rhabdomyosarcoma 8900/3
    l) Chondroma 9220/0
    m) Osteoma 9180/0
    n) Osteochondroma 9210/0
    o) Chondrosarcoma 9220/3
    p) Osteosarcoma 9180/3
    q) Haemangioma 9120/0

r) Epithelioid haemangioendothelioma 9133/1

s) Angiosarcoma 9120/3

t) Kaposi sarcoma 9140/3

u) Ewing sarcoma-peripheral primitive neuroectodermal tumour 9364/3

- Hemangiopericytoma

  a) Haemangiopericytoma 9150/1

  b) Anaplastic haemangiopericytoma 9150/3

- Melanocytic lesions
- Hemangioblastoma

  Haemangioblastoma WHO Grade I 9161/1

The WHO classification of the tumours of the CNS 2007 classifies meningioma into three grades and thirteen histological subtypes. The three grades are

1. Grade I – Benign
2. Grade II – Atypical
3. Grade III – Anaplastic or Malignant

GRADE I MENINGIOMAS:

Meningiomas are most commonly benign or Grade I. Even though there are various histological subtypes for benign meningiomas the treatment and prognosis doesn't differ much in them.

The subtypes that are more common are

- Meningothelial Meningioma 9531/0
- Transistional meningioma 9537/0
- Fibrous Meningioma 9532/0

Followed by other common subtypes such as

- Psammomatous Meningioma 9533/0
- Angiomatous Meningioma 9534/0
- Microcystic Meningioma 9530/0
- Secretory Meningioma 9530/0
- Lymphoplasmocyte rich Meningioma 9530/0
- Metaplastic meningiomas Meningioma 9530/0

CYTOLOGY:

Intraoperative smear preparation is helpful to demonstrate the cytological features of meningioma.The cells are round to oval.Nuclear feature are distinctive.They are slightly oval nuclei with a delicate

euchromatin with inconscpicous nuclei.The most characteristic feature is the presence of intranuclear inclusions.These inclusions are also called as “orphan annie eye”inclusion. Two forms of nuclear inclusions are seen.

1)sharply defined pinkish or eosinophilic cytoplasmic inclusion

2)Diffuse washing out of nuclei .

Other characteristic feature that points to a diagnosis of meningioma are whorls and psammoma bodies.cellular whorls are colletions of cells arranged in concentric lamellated fashion.cells in the centre of the whorls are more polygonal whereas cells in the outside of whorls are elongated .These whorls are tight to loosely wound clusters.on intraoperative smear preparation these tight cellular whorls are clues to the diagnosis of meningioma.however these whorls are not pathognomonic of meningioma as these can be seen in other tumours as in schwannoma. Psammoma bodies are concentric lamellated calcifications .these calcification initially appear in the centre of the whorls.These can range from punctate tiny deposits to large calcifications.however these are not diagnostic of meningioma as it seen in tumours like schwannoma,metastatic tumours.

GRADE I MENINGIOMAS [25]:

1)MENINGOTHELIAL MENINGIOMA:

Also called as synctial meningioma.Histologically composed of clusters of meningeal cells which have a synctial appearance due to tight interdigitating cellular processes.Individual cells have round to oval nuclei with finely stippled chromatin eith small indistinct nucleoli.Few of the nucleus exhibit nuclear psudoinclusions.psammoma bodies and whorls are sparse often.

Differential diagnosis:

a)Meninioangiomatosis,

b)Arachanoidal hyperplasia.

c)Melanocytic neoplasm:

They have a more prominent nucleoli,with a clearly well defined cytoplasmic margins.It is frequently immunoreactive for S-100 and HMB-45.EMA is always negative.On ultrastructural examination it may contain melanosomes.

d)Glioma:

They have a diffuse pattern of brain infiltration,with positive immunoreactivity for GFAP.It is not immunoreactive for EMA.

2)FIBROUS/FIBROBLASTIC MENINGIOMA:

On gross examination these lesions exhibit a rubbery ,firm texture.On microscopic examination they show mesenchymal differentiation with spindle cells arranged in storiform pattern and in wide fascicles in a thick collagenized matrix.The fascicles are more organized than in schwannoma which have more haphazard pattern.Rarely "amianthoid fibres" which are collagen fibres that accumulate in a stellate form.

Differential diagnosis:

a)Schwannoma:

They show a pericellular reticulin distribution.

b)Pilocytic astrocyoma,

c)Fibrillary astrocytoma,

d)Solitary fibrous tumour.

Collagenous bundles differentiates this from schwannoma and astrocytoma.

3)TRANSITIONAL MENINGIOMA:

They exhibit features of both synctial and fibrous meningioma.Prominent meningeal whorls and psammoma bodies makes

them easiest to diagnose with hematoxylin &eosin.vague lobular and fasicular arrangements are seen along with these psammoma bodies and tight whorls.

Differential diagnosis:

Pilocytic astrocytoma,

Schwannoma

4)PSAMMOMATOUS MENINGIOMA:

These tumours are characteristically seen in the thoraco spinal region of a middle aged female. In this subtype psammoma bodies is seen predominantly over that of meningothelial cells. Psammoma bodies are lamellated calcospherules.unusually these psammoma bodies can become confluent with tumour meningothelial cells being difficult to find. occassional bone formation can be seen.

Differential diagnosis:

Psammomatous schwannoma,

Metastatic adenocarcinoma with psammoma bodies.

4)ANGIOMATOUS MENINGIOMA:

In this variant there is large number of vascular channels which are small to medium sized ,thin walled or thick hyalinized walls. Nuclear

atypia which are degenerative in nature can be moderate to marked. Adjacent cerebral parenchyma exhibit cerebral edema which can be out of proportion to the tumour size.[26]

Differential diagnosis:

a)Hemangioblastoma :Shows a characteristic arrangement of capillaries and stromal cells.EMA and vimentin is negative.On electron microscopy no desmosomal junctions are seen.

b)Vascular malformations: Arterio venous malformation shows an absence of menigothelial cell nests.

c)Hemangiopericytoma

4)MICROCYSTIC MENINGIOMA:

As the name implies there are many microcystic spaces which contain eosinophilic ,pale mucinous fluid. Fluid is derived from the transduation of plasma across the stromal vasculature which are frequently hyalinized.cells exhibit cytoplasmic clearing due to lipid/glycogen accumulation.Numerous pleomorphic cells are seen which are degenerative in nature are seen.however this variant is benign in their behavior.It has also been referred to as “Humid meningioma”(Forme humide of Masson)

Differential diagnosis :

a)Low grade microcystic astrocytoma,

b)Hemangioblastoma.

Features like nuclear hyperchromasia,plemorphism and nucleomegaly suggest this differential however there is no mitotic activity which excludes microcystic astrocytoma.

5)SECRETORY MENINGIOMA:

Histologically these are composed of pseudopsammoma bodies. These are epithelial cells with intracellular lumina containing eosinophilic PAS positive secretion which are hyaline globular inclusions. Mast cells are numerous. peritumoural cerebral edema is prominenent.

Ultrastructuraly these spaces are microvillus lined spaces.Immunohistochemical evaluation shows a positivity for IgA,IgM.Carcinoembryonic antigen immunoreactivity is seen in these secretions.CEA levels rise with recurrence hence used to monitor patients.

Differential diagnosis:

a)Metastatic carcinoma:Cells have more clearly defined margins,with more anaplasia and increased mitoses.Carcinomas are more commonly cytokeratin positive.

6)LYMPHOPLASMACYTE –RICH:

This is the rarest of all the variants showing extensive chronic inflammatory cell infiltrates composed of lymphocytes and plasma cells. These inflammatory cells can be so numerous that it can obscure the underkying meningeal tumour.Associated systemic abnormalities like hyperglobulinemia and refractory iron deficiency anemia is documented in few cases[27].

Differential diagnosis:

Primary hematopoietic processes

7)METAPLASTIC MENINGIOMA:

Meningioma composed of mesenchymal elements like osseous,lipomatous,cartilaginous,xanthomatous or myxoid tissue which can be focal or widespread.

Differential diagnosis:

Primary mesenchymal lesions .eg. Osteoma

8)SCLEROSING MENINGIOMAS:

These tumours are frequently seen in pediatric age group. There is progressive fibrous obliteration with few of the foci exhibiting pleomorphism, hyperchromasia. However these belong to WHO Grade 1 tumours. [28],[29]

GRADE II MENINGIOMA:

The subtypes in this are as follows

Atypical meningioma 9538/1

Clear cell meningioma 9538/1

Chordoid meningioma 9538/1

ATYPICAL MENNGIOMA:

They constitute about 4-7% of meningiomas. Increased mitotic activity is the characteristic feature i.e about 4 to 19 mitoses per 10 hpf. Brain invasion is an independent criterion of Atypical meningiomas. In tumours with less mitotic activity to be classified as Grade II it must have three or more of the following features. [30]

1. Increased cellularity
2. Small cells with high nucleus to cytoplasm ratio
3. Prominent Nucleoli

4. Uninterrupted patternless or sheet like growth
5. Spontaneous or geographic Necrosis

1)Hypercellularity:

Hypercellular regions denote areas in which there is “small cell formation” that is cells with increased nuclear cytoplasmic ratio ,hyperchromatic nuclei,with scant cytoplasm.

2)Lack of classic architectural pattern:

Three classic patterns are seen which includes

a)lobular in meningothelial,

b)Fasicular in fibrous,

c)Whorling in transitional and other forms.

Lack of these characteristic pattern prompt us to the diagnosis of atypical meningioma.”Sheeting” occurs in atypical meningioma in which tumour cells form large sheets devoid of whorls or fascicles.one of the helpful feature in evaluating sheeting is evaluation of cytoplasmic borders.The crisp and distinct cytoplasmic borders suggest that sheeting is real.

3)Necrosis:

Three patterns of necrosis is commonly encountered.

1)Large , geographic areas of necrosis which can be ischaemic or infarctive in nature

2)Multifocal ,small areas of necrosis with cellular debris.

3)Single cell death

However multifocal centrilobular form of necrosis is highly characteristic of atypical meningioma.Perinecrotic pseudopalisading is seen sometimes leading to misinterpretation as glioblastoma.Preoperative embolisation lead to large geographic ,infarctive type of necrosis.

4)Mitotic activity:

Benign meningiomas has some scattered mitotic figures but these are not atypical mitotic figures.

Clear cell meningioma and Choroid meningiomas are rare subtypes of atypical meningiomas. Choroid meningioma resembles to chordoma histologically.

2)CHORDOID MENINGIOMA:

These are composed of cords and trabeculae of eosinophilic ,vacuolated cells in a abundant mucoid background.they resemble

chordoma hisologically but can be differentiated by their meningothelial nuclei and whorl formation.castlemans disease is infrequently associated with chordoid meningioma. [31]

Differential diagnosis:

chordoma

3)CLEAR CELL MENINGIOMA :

They exhibit predilection for young adults including children and are most often found in the cerebellopontine and cauda equina region. These extracranial dural based lesion are patternless meningioma with polygonal cells containing water clear cytoplasm ,which are glygogen rich showing PAS positive ,diastase resistant reactivity. psammoma bodies are not seen in this variant. Higher rates of recurrence ,frequent CSF seeding,increased moratality characterize this aggressive variant. [32]

Differential diagnosis:

Oligodendroglioma

Central neurocytoma

Clear cell ependymoma

GRADE III MENINGIOMA:

Anaplastic meningioma 9538/3

Rhabdoid meningioma 9538/3

Papillary meningioma 9538/3

1)ANAPLASTIC MENINGIOMA:

This constitute 1-3% of all meningiomas. It tends to occur in relatively younger age groups with male predominance.

a)They have high mitotic index ie about 20 mitosis per 10 HPF or

b)meningoepithelial differentiation is lost with appearance resembling sarcoma, carcinoma or melanomas.[30]

Differential diagnosis:

Metastatic carcinoma

Metastatic melanoma,

Sarcoma

They are prone for local recurrence and distant metastasis. Some rare subgroups included in Grate III are rhabdoid and papillary meningiomas.

2) PAPILLARY MENINGIOMA:

These are characterized by perivascular ependymoma like clustering of tumour cells around the vasculature. conventional

meningothelial regions are almost identifiable but they exhibit increased cellularity,mitoses,and foci of necrosis.local invasion and brain invasion is noted in 75% cases,recurrence in 55% cases.and lung metastasis in 20 % cases.[33].

Differential diagnosis:

Metastatic papillaryadenocarcinoma,

Malignant melanoma,Ependymoma,Choroid plexus tumours.

3)RHABDOID MENINGIOMA:

These correspond to clinically aggressive grade 3 meningioma. Histologically composed of sheets of rhabdoid cells which are large cells with abundant cytoplasm containing globose,inclusion like bodies which are cytoplasmic vimentin filaments and eccentric nucleus,open chromatin and a prominent nucleolus. Brain invasion and increased mitoses is the rule.[34]

Differential diagnosis:

Metastatic rhabdoid tumour

Metastatic carcinoma

Metastatic melanoma

Malignant glioma

Atypical rhabdoid/teratoid tumour

Rhabdomyosarcoma

Oncocytic meningiomas:

These cells exhibit cytoplasmic fine granularity due to increased number of mitochondria.

Differential diagnosis:

Oncocytic tumours

BRAIN INVASION AND METASTASIS:

Most meningiomas indent the underlying brain parenchyma however about ¼ of cases show brain invasion.

Gross: Attention should be paid to the presence of cerebral tissues.

Microscopy:

It can occur in benign,atypical,anaplastic meningioma.It denotes high rates of recurrence. brain invasion does not alter the grade of meningioma.

Two patterns of invasion is seen:

1) It is characterized by broad nodules of tumour invading Virchow robins spaces superficially with mild gliosis of the adjacent parenchyma.

However this pattern of involvement warrants the clinician for close follow up. Also this does not mean the tumour is malignant

2) These are characterized by irregular tongue like extensions infiltrating the underlying cerebral parenchyma. This denotes an aggressive /malignant behavior of the tumour.

Genetically these lesions exhibit ch.1p and 14q deletions .entrapped brain parenchyma are GFAP positive against the GFAP negative tumour extensions.

METASTASIS:

The common sites for metastasis include lung,liver,pleura,bone. metastasis denotes a tumour as malignant.there is an entity known as "benign metastasizing " meningioma in which a histologically benign meningioma is associated with a histologically benign metastasis in liver or lung. Excision is the treatment of choice. Recurrences are rare.

2)Involvement of local sites do not qualify a tumour as malignant. It means meningioma with involvement of overlting skin or skull does not mean a tumour as malignant.

3)Invasion of dural sinuses also does not mean a tumour as malignant. However the extensive local spread of tumour will be difficult to resect and hence more prone for recurrence.

4)Extracranial meningiomas :

These should not be mistaken for metastasis.These cases has no intracranial lesions. Sites favoured for extracranial sites include

a.Skin

b.Lung

c.Nasal cavity

d.Paranasal sinuses

e.Oral cavity

f.Parotid gland

g.Ear

h.Mediastinum

i.Soft tissues of neck

j.Peripheral nerves

These extracranial meningiomas are characteristically meningothelial meningiomatous type.most are benign grade 1 tumours which are treated with excision.

Bony invasion through osseous canaliculi is not a sign of malignancy.

Mahmood et al in his study has laid down criteria for grading of meningiomas.

- GRADING OF NUCLEAR PLEOMORPHISM:

  Grade 0-Tumour cells with uniform nuclei, dense chromatin and inconspicuous nucleoli.

  Grade 1-occasional tumour cells show nuclei that is 2-3 times enlarged with irregular nuclear contours

  Grade 2- Predominant cells with nuclei larger than meningothelial nuclei with pale chromatin with small or absent nucleoli.

  Grade 3- vesicular nuclei with single or multiple prominent nucleoli .

- GRADING OF HYPERCELLULARITY:

  Grade 0 – tumor entirely composed of meningothelial whorls/10 hpf. Tumor cells are large with vesicular chromatin and abundant cytoplasm.

  Grade 1-tumour is predominantly composed of whorls with perivascuar areas having smaller cells and loss of pattern.

  Grade 2-predominantly composed of smaller and less defined whorls.

Grade 3-cells tightly packed with overlapping nuclei and scant cytoplasm. No distinct whorl formation seen.

- GRADING OF MITOTIC FIGURES:

  Grade 0 – no mitoses/10 hpf

  Grade 1 1-2 mitoses/10hpf

  Grade 2 3-4mitoses/10hpf

  Grade 3 >=5 mitoses/10 hpf

- GRADING OF NECROSIS:

  Grade 0 – no necrosis

  Grade 1- small foci of necrosis involving only less than of a high power field.

  Grade 2- necrosis involving less than one high power field.

  Grade 3-large confluent necrosis involving more than one high power field.

- GRADING OF LOSS OF ARCHITECTURE:

  Grade 0- no sheeting architecture.

  Grade 1- incipient loss of fascicular arrangement of tumor cells.

  Grade 2 - readily identifiable loss of pattern involving one to two high power fields.

  Grade 3 – large areas of solid pattern involving several high power fields.

ELECTRON MICROSCOPY:

Diagnostic features include

a)abundant intermediate (vimentin) filaments

b)tight intercellular desmosomal junctions

c)complex interdigitation of tumour cellular processes without basal lamina material.

Secretory varisnt show single or even multiple epithelial like intarcellular lumina with single meningothelial cell.these cells exhibit short apical processes surrounding electron dense secretions.

Microcystic meningiomas show intercellular electron lucent matrix enclosed by cytoplasmic processes which are bound by desmosomes.

IMMUNOHISTOCHEMISTRY:

Majority of meningiomas typically stain for EMA with a characteristic membranous positivity or have diifuse cytoplasmic positivity.EMA positivity distinguish meningiomas from gliomas and schwannomas and hemangiopericytoma.Vimentin positivity is strong in all meningiomas. S100 is variably positive.It is useful in distinguishing meningiomas and schwannomas as schwannomas are strong S100 positive. CEA(Carcinoembryonic antigen) is strongly positive in

secretory meningiomas. other markers which are expressed include progesterone receptors,Ki67.claudin is expressed in some of the cases. NCAM(Neural cell adhesion molecule) is strongly expressed in fibroblastic meningiomas. Types I,III,IV,V collagens and laminin are found in fibrous tumours.Endothelin 1 and endothelin receptors ET-Ar ,ET-Br and PDGF,IGF are also expressed in meningiomas.

RECURRENCE RATE :

Meningioma Grade	**Incidence %**	**Recurrance rate**
Grade I	>90% Benign with less aggressiveness.<4mitoses/10hpf	7-25%
Grade II	4-7% Atypical with 4-19 mitotic activity/10hpf. Three or more of the following features such as increased cellularity, small cells with increased nucleus cytoplasmic ratio, prominent nucleoli, sheet like growth and focal or geographic necrosis.	29-50%
Grade III	1-3% Anaplastic with histologic features of malignancy. They more commonly cause invasion.	50-94%

Predicting the recurrence rate and behavior of meningioma cannot be made solely on the basis of histopathological examination.7 to 20 % of benign grade 1 meningiomas are known for their recurrence.studying the

proliferation index provides a objective method of assessing tumour recurrences.[35]

PROLIFERATION INDEX:

Ki-67 is an antigen expressed in proliferating cells throughout the cell cycle. MIB-1 is the antibody which targets the antigen Ki-67 and hence it is used in the measurement of Proliferation index.Ki67 is expressed in the proliferative phase of the cycle(G1,S,G2,M phases of the cell cycle). Hence it is a reliable marker for assessing tumour growth and behavior.likewise MIB 1 labellling indices are used to indicate tumour proliferation rate and to plan the adjuvant therapy accordingly.[36]

If there increased MIB-1 staining index then it represents higher histological grade aand increased risk for recurrence. Many studies have reported that for recurrent meningiomas there will be a high Proliferation Index compared to less aggressive ones.[37]

Meningiomas having MIB-1 staining index of >4% then the propensity for recurrence of the meningioma is significantly higher. Various studies has shown that MIB-1 staining index is more in meningiomas with evidence of edema in MRI's and in Males compared to females. According to Matsuno et al., 1996 in meningiomas with calcifications the MIB-1 staining index is comparatively lower.

LABELLING INDEX:

Labelling index represents the percentage of immunoreactive tumour cell nuclei. In determining labeling index tumour sampling may be the source of error because there will be histological heterogenicity with regional differences in cell proliferation. Because of this the labeling index should be analysed from the region of the tumour that is histologically most malignant. The Labelling index is higher for meningiomas in Neurofibromatosis patients depicting the more aggressive behavior of these meningiomas . The labelling index of various grades of meningiomas are as following table.[38]

Meningioma Grade	Labelling Index
Grade I	3%
Grade II	8%
Grade III	17%

MOLECULAR GENETICS:

Merlin is a tumour suppressor which is located on the cell membranes and it regulates cell to cell contact and motility. This Merlin tumour suppressor is encoded in the NF2 gene which is located in chromosome 22. The absence merlin tumour suppressor results in

increased cell proliferation in meningioma cells. The most common gene alteration in meningioma is monosomy of chromosome 22. Inactivation of this merlin gene is responsible for occurance of 60% of sporadic meningiomas and for the rest of 40% of sporadic meningiomas the genetic background is not known. Deletions of short arm of chromosome 22 (22q) is present in almost 100% of cases of Neurofibromatosis patients. The frequency of gene alterations vary among different subtypes of benign meningiomas.

NF2 mutations occur in 70-80% of fibroblastic and transitional subtypes whereas only 25% of meningothelial subtype have NF2 mutations. The frequency of NF2 mutations doesn't vary in different histological grades and hence these mutations are presumed to occur in early part of tumorigenesis.

DAL-1 protein is also a transmembrane protein with tumour suppressor properties resembling merlin. The gene for DAL-1 protein is located in chromosome 18. In 76% of sporadic meningiomas the DAL-1 expression is lost. Similar to merlin the loss of expression of DAL-1 protein is similar among different histiological grades of a subtype indicating it as an early event in tumorigenesis.

Deletions in chromosome 1 has been associated with tumour progression. According to Bello et al., 1994 only 13-26% of benign

meningiomas represents 1p deletions where in anaplastic variant the 1p deletions is found in 70-100% signifying its role in tumour progression. Similarly deletions in chromosome arm 14q has increasing frequency from low grade to high grade representing its role tumour progression.

Cytogenetic features of meningiomas differ among males and females. The frequency of abnormalities in Chromosome 22 and X are more common in females compared to males whereas the frequency of monosomy 14 is higher in males. Loss of chromosome X is found in 14% of female patients. 25% of male patients show chromosome Y nullisomy.

Non-steroid hormone associated genetic factors which are encoded in the sex chromosomes may be involved in the development of meningioms. Differential classification of meningioma between males and females can be done based on eight genes which are differentially expressed among males and females[39]

GENETIC ALTERATIONS:

BENIGN:

- NF2 gene mutations and chromosome 22 q loss
- Ch Y loss
- Ch 1p and 3 p loss
- Ch 9q mutations

ATYPICAL/MALIGNANT:

- Ch 1p loss
- Ch 10 loss
- Ch 14 q loss
- TP53 mutations
- CDKN2A/p16 gene deletions
- Ch 6q,9q,18q loss
- Ch 17q23 amplification
- Ch 1 q,9q,12q,15q,17q,20q gains

SEX HORMONE RECEPTORS IN MENINGIOMAS:

Progesterone is a steroid hormone which is involved in fertility of females, preparation of endometrium of uterus for the implantation of embryo and in maintainence of pregnancy. Hence it is named as the 'Steroid hormone of reproduction'.

Besides the specific effects on endometrium the progesterone hormone also has some antiestrogenic and antiproliferative effects on other tissues. This lead to new interests in this hormone because of its effect in proliferation the progesterone hormone with its synthetic agonists and antagonists can be used in cancer therapy.

The action of progesterone is through the progesterone receptor and hence the study into the detailed function and regulation of these progesterone receptors will help in the management of tumours expressing these receptors.

Meningiomas are presumed to be hormone sensitive tumours because of the following facts

1. Higher incidence of meningiomas in females than males.
2. Meningioma and breast cancer association epidemiologically.
3. The reduced aggravation of symptoms of meningiomas during pregnancy and luteal phase of menstrual cycle which are periods of relative progesterone excess indicating the effect of progesterone in these tumours.

But during pregnancy there may be increase in size of meningiomas which is due to cellular edema and not because of increased proliferation.

After the report of presence of ER in meningioma tissue various studies has been conducted based on this subject. Many studies have reported both ER and PR positive in meningiomas but some studies revealed ER negative and PR positive phenotype. This may be explained

by the methodological differences of assay of tumour tissue for ER receptors since many studies used single-point binding assays which is less reliable than the Immunohistiochemistric or enzyme-immuno analysis.

Even though the presence estrogen receptors could be demonstrated in some meningiomas it is present at a very low level compared to breast cancer in which there is more expression of ER receptors. The meningiomas shows ER negative and PR positive as predominant phenotype compared to Breast cancer which shows both ER and PR positive phenotype.

PROGESTERONE RECEPTOR :

The presence of Estrogen and Progesterone receptor in meningiomas was first described by Donnel et al in 1979.In the intial days only receptor binding assays were only available to detect the Estrogen and Progesterone receptor which produced cumbersome results due to diiference in interpreting the results based on level of cytosolic receptor binding sites. However with the advent of monoclonal antibodies,detection of ER,PR is made easy, reliable and rapid using immunohistochemical techniques.

The action of progesterone is mediated through progesterone receptors. The receptors for steroid hormones, retinoic acid and thyroid hormones along with orphan receptors form a super family of transcription factors. The characterization of specific functional domains in these proteins are conserved within a species and among family members. [40].

The location of progesterone receptor is mainly in the nucleus which is maintained by a balance between a continuous active transport into the nucleus and diffusion into the cytoplasm of these receptors. The active transport of the progesterone receptor into the nucleus is done by Nuclear localization signal.

The receptors contain two domains of which the DNA Binding Domain is highly conserved whereas the the carboxy-terminal which is the Ligand Binding Domain is less conserved. This Ligand Binding Domain contains a region called Activation function 2 (AF-2) which is ligand dependant. The amino terminal of the receptor contains a region called Activation function 1(AF-1) which is ligand independent.

Both AF-1 and AF-2 act in a synergestic manner which is required for receptor function. Another domain region called AF-3 which is a strong autonomous activation domain function in a restricted cell and promoter context.

The unliganded progesterone receptor is inactive and is attached with Heat shock proteins. When the ligand binds to the receptor it initiates a series of events as follows.

1. Ligand binds to the progesterone receptor.
2. The Heat shock proteins gets dissociated from the receptor.
3. The tertiary structure of the receptor protein changes.
4. Phosphorylation, dimerization and high affinity binding to progesterone responsive elements causes the activation of the receptor.
5. The activated receptor interacts with Transcription machinery complex and initiates the transcription of progesterone responsive genes.

The activation of the transcription also requires some regulatory proteins called cofactors. Two isoforms of progesterone receptor exists which are PR-A and PR-B.

The PR-B isoform has an additional stretch of 164 amino acids at the amino terminus which is called B Unique Sequence (BUS). The BUS region which encodes the AF-1 is specific to the PR-B isoform that plays a main role in specific target gene activation that cannot be activated by PR-A isoform.

The isoforms after binding with progesterone dimerize and interact with Progesterone responsive elements and also activate transcription which regulate PR target gene expression. When the isoforms are present in equimolar concentrations the dimerization can occur in three ways, A:A, B:B homodimers and A:B heterodimers each of which have different gene regulating properties. Thus in response to progesterone both PR-A and PR-B isoforms can regulate different physiological target genes since they have different transactivation capacities. In certain cell contexts the PR-A is capable of repressing PR-B transactivation and also Estrogen Receptor.

Thus PR-A isoform has the ability decrease the responsiveness of specific target genes by progesterone. Thus in treating benign breast diseases with progestins the differential expression of PR isoforms is important clinically. Thus in the treatment of meningiomas with progesterone derivatives the evaluation of the differential expression of isoforms of the progesterone receptors would be very helpful.

PR negative meningiomas are of more aggressive nature than progesterone receptor positive ones. Expression of progesterone receptors even in a small number of tumour cells is considered as a favourable prognostic factor as said by Hsu et al 1997.[37]

ESTROGEN RECEPTOR:

The expression of estrogen receptor is absent in normal meningial tissues. Estrogen receptor expression is found in approximately one third of meningiomas. It is also said that no relationship exists between estrogen and progesterone receptor expression in meningiomas.

Estrogen receptor expression in meningiomas is associated with more aggressive behaviour. Meningiomas that have progressed from Benign to Atypical types had Estrogen receptor Expression of 30% compared to de novo atypical meningiomas in which estrogen receptor expression is 0%. [41]

MANAGEMENT :

SURGERY:

As in cushings day ,surgery is the mainstay of treatment. Hence degree of resection is an important predictor of tumour recurrence. However complete resection is not possible in case of radiation induced meningioma as they are multiple and invasive lesions.

Also the thin atrophic skin further limits the surgical option in previously irradiated patients presenting with radiation induced meningioma.

RADIOTHERAPY:

This has a definitive role in reducing recurrences in post operative patients.various modalities are which are as follows

Streotactic radiotherapy,intensity modulated radiotherapy,fractionated radiotherapy,and protons.

HORMONES:

Newer anti hormonal approaches have been developed based on promising results of breast cancer treatment.curently patients with progreesive disease following primary radiotherapy or post operative radiaton is treated with endocrine therapy. Mifepristone an oral anti-progestational agent is tried. According to edwards et al mifepristone acts by inhibiting transcriptional activity of progesterone receptor by a complex mechanism at concentration much lower than progestins.

Olson et al assessed the efficacy of mifepristone therapy in meningioma specimens which caused an inhibition of growth in vitro. These results encouraged the endocrine therapy as an alternative mode of therapy for unresectable and recurrent meningiomas.

Tamoxifen is an oral ER modulator that binda to ER producing nuclear complexes that inhibits DNA synthesis and thereby inhibit estrogen [(42)].

MATERIALS AND METHODS

MATERIALS AND METHODS

STUDY DESIGN:

Cross sectional study

PLACE OF STUDY:

Department of Pathology, Coimbatore Medical College Hospital, Coimbatore

STUDY PERIOD:

July 2013-July 2014

INCLUSION CRITERIA:

1.All meningioma specimens received in the Department of pathology.

2.Well fixed adequate tissue

EXCLUSION CRITERIA:

1.Inadequate tissue for multiple sectioning

2.Ill fixed specimen

Sections were cut at four micron thickness on to a coated slides which are then incubated at 58 degrees overnight.Initial sections were stained with hematoxylin and eosin stain.

HEMATOXYLIN & EOSIN STAINING METHOD:

REAGENTS USED:

1.Hematoxylin solution-Erhlich's hematoxylin

2.EosinY 1% solution

3.Acid alcohol 1% solution

PROCEDURE:

1.Deparaffinize sections in xylene by immersing for 30 seconds.

2.place the sections in Isopropyl alcohol for 15 minutes

3.Wash in running tap water

4.stain in Erhlich's hematoxylin for 10 to 15 minutes

5. wash in running tap water

6.Differentiation is done with 1% acid alcohol-two to three dips

7.blueing is carried out for 10 minutes.

8.Counterstain with eosin 1% solution-3 to 4 dips

9.Running tap water wash

10.Air dry

11.Mount with DPX

The sections are studied based on histomorphological features and a diagnosis is obtained.

IMMUNOHISTOCHEMISTRY:

METHODS:

Two step indirect technique

PRINCIPLES OF IMMUNOHISTOCHEMISTRY:

This technique relies on detection of antigens expressed the cells and tissues with the two step process

1.Primary antibody is bound to antigens using specific epitopes

2.Calorimetric reaction that follows detects the antigen antibody binding.

REAGENTS:

1.Peroxide block: Hydrogen peroxide 3 % in water

2.Power block: This is an effective protein blocking reagent.It contains casein and properity additives with 15 mM sodium azide in PBS

3.Chromogen: DAB- 3 3’ diaminobenzidine

4.Liquid DAB substrate: Tris buffer containing stabilizers and peroxides.

5.Super Enhancer

6.Mayers hematoxylin is used to counterstain.

7.Buffer solutions

TRIS BUFFER(pH 7.6)

TRIS buffer salt:0.605grams

Nacl :8 grams

Distilled water :1 litre

1N HCL :3 ml

CITRATE BUFFER(pH 6.0)

Trisodium citrate: 2.94 grams

Distilled water :1 litre

1N HCL:5 ml

TRIS EDTA:(pH 9.0)

TRIS Buffer salt:6.05 grams

Disodium EDTA:O.744 grams

Distilled water: 1 liter

PROCEDURE:

1.Deparaffinise sections in xylene for 30 minutes

2.keep in absolute alcohol for 10 minutes

3.wash in running tap water for 10 minutes

4.Dip in distilled water for 5 minutes

5.Antigen retrieval done by placing slides in microwave with appropriate buffer solutions.

6.Cool the sections to room temperature

7.Rinse the sections in distilled water

8.TBS buffer wash-5 minutes 2 changes

9.Peroxide block for 10 minutes

10.TBS Buffer wash – 5 minutes 2 changes

11.power block -10 minutes

12.Primary antibody is used to cover the sections(supplied by DAKOCYTOMATION)

13.TBS Buffer wash-5 minutes 2 changes

14.Cover the sections with Super Enhancer for 30 minutes

15.TBS Buffer wash -5 minutes 2 changes

16.Apply poly HRP reagent for 30 minutes

17.TBS Buffer wash -5 minutes 2 changes

18.Trat with DAB chromogen and substrate buffer for 5 to 8 minutes

19.TBS Buffer wash 5 minutes 2 changes

20.Wash the slides in running tap water for 5 minutes

21.Counterstain in Mayers hematoxylin -1 minute

22.Tap water wash for 5 minutes

23.Air dry, mount in DPX.

Positive control for progesterone and estrogen receptor includes breast cancer slides that is ER,PR immunoreactive. Positive control for Ki67 includes lymph node that is immunoreactive for Ki67. Negative control was also run each time

Immunohistochemical evaluation:

The entire sections in a slide is examined under high power objective for the presence of positive immunoreactivity. Tumour cells are read positive if there is golden brown nuclear staining of the neoplastic cells. Semiquantitative scoring was carried out.

Grading of intensity staining:

0-absent

1-weak

2-moderate

3-strong

Percentage of positive tumour cells:

0-absence of positive tumour nuclei

1-10% of cells are positive

2-10-50% of cells are positive

3-51-80% of positive tumour cell nuclei

4->80% are positive tumour cell nuclei

Progesterone receptor was read as positive if >10% of cells shows strong immunostaining or >50% of cells show moderate staining. For Ki 67 labelling index each slide was examined under high power and hot spot was selected. Hot spot is an area with highest immunostained nuclei. 1000 tumour cell nuclei was counted and the labelling index was expressed as percentage of positive cells. Caution should be expressed while interpreting Ki67 positivity as any proliferating cell such as

lymphocytes can be positive.Hence hot spot should always be selected after meticulous comparision with routine H&E sections.

Data:

Tumour was subtyped according to new WHO classification using H&E sections. Patient age, gender, progesterone receptor , estrogen receptor status,Ki67 was determined and expressed.

Statistical analysis:

SPSS software version 15 was used for analysis and the variables were expressed as percentage of number (percentage %).Chi square tests was employed for statistical comparisons. P value <0.05 was considered statistically significant.

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OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

The present study is a prospective study conducted in the Department of Pathology,Coimbatore Medical college Hospital. A total of 30 cases of meningioma specimens received over the period of July 2013 to July 2014 were studied.

Ethical clearance was obtained from Ethics committee of Coimbatore Medical College and Hospital,Coimbatore.

Histomorphological and immunohistochemical pattern of expression was studied , analysed and compared with the literature.

TABLE 1

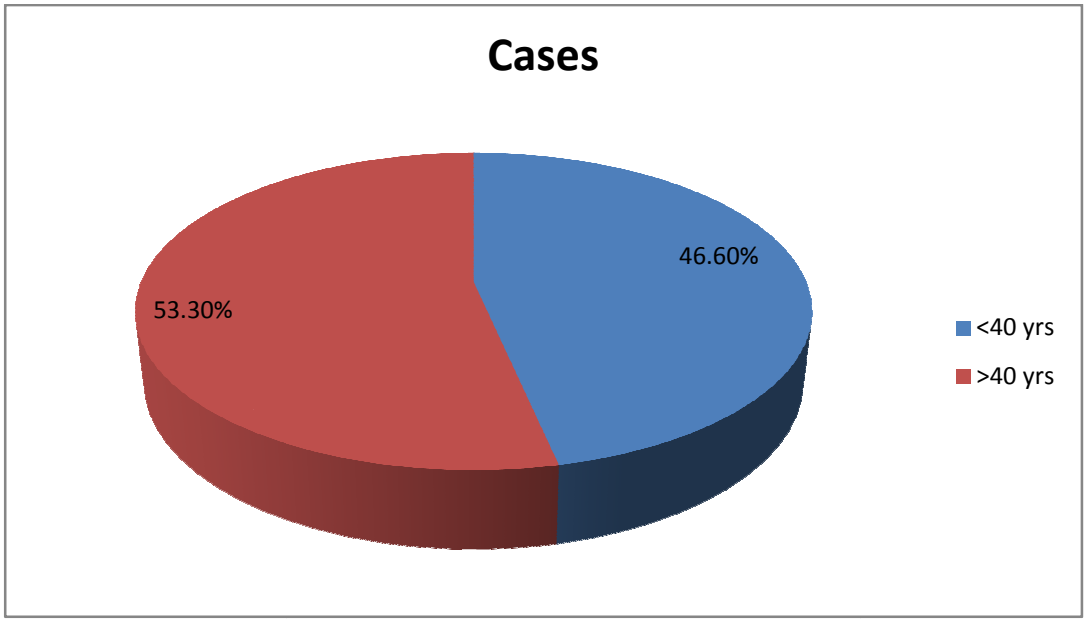
AGE WISE DISTRIBUTION OF MENINGIOMAS(n=30)

AGE	CASES
<40 YEARS	14(46.6%)
>40 YEARS	16(53.3%)

In the present study out of total 30 cases, 14 cases were <40 years which constitutes around 46.6% and 16 cases were in age group >40 years which constituted around 53.3%.Patients age group ranges from 27-75 years with mean age of 45 .7 +/- 13.1 years .

CHART 1

AGE DISTRIBUTION OF MENINGIOMAS (n=30)



As noted from above Pie chart , in the current study ,age group >40 years were higher with 53.3% than age group <40 years which was only 46.6% .Mean age of patients in the present study was 45 .7 +/- 13.1 years .

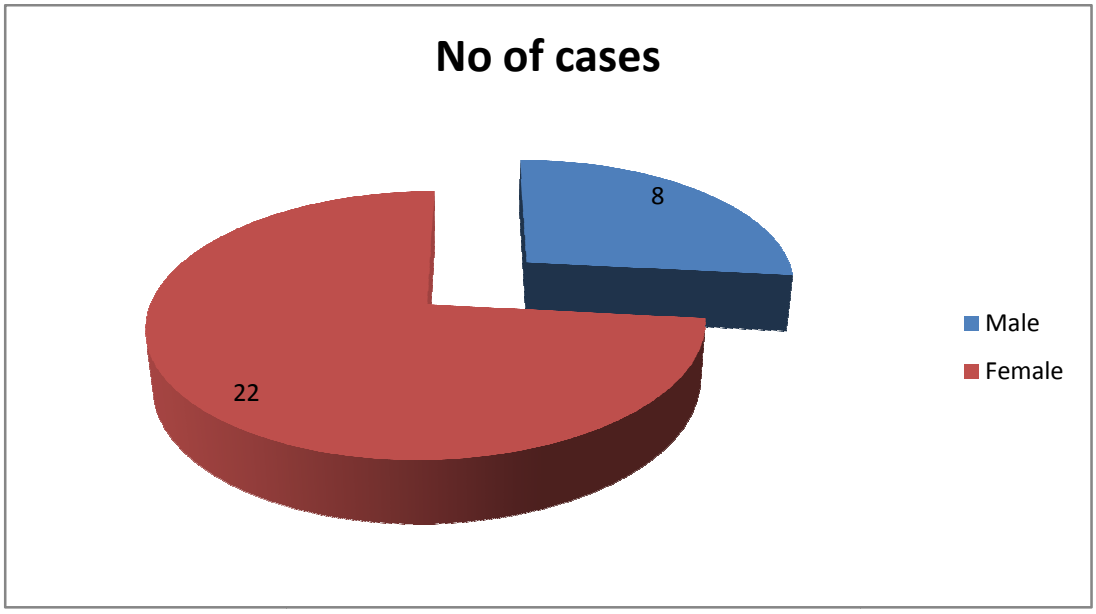
CHART 2

SEXWISE DISTRIBUTION OF MENINGIOMAS

TOTAL CASES: 30

MALES: 8 CASES (27%)

FEMALES: 22 CASES (73.3%)



In the present study females constituted around 22 cases(73.3%) outnumbering males which were 8 cases(27%).

FEMALE:MALE RATIO: 2.7:1

TABLE 2

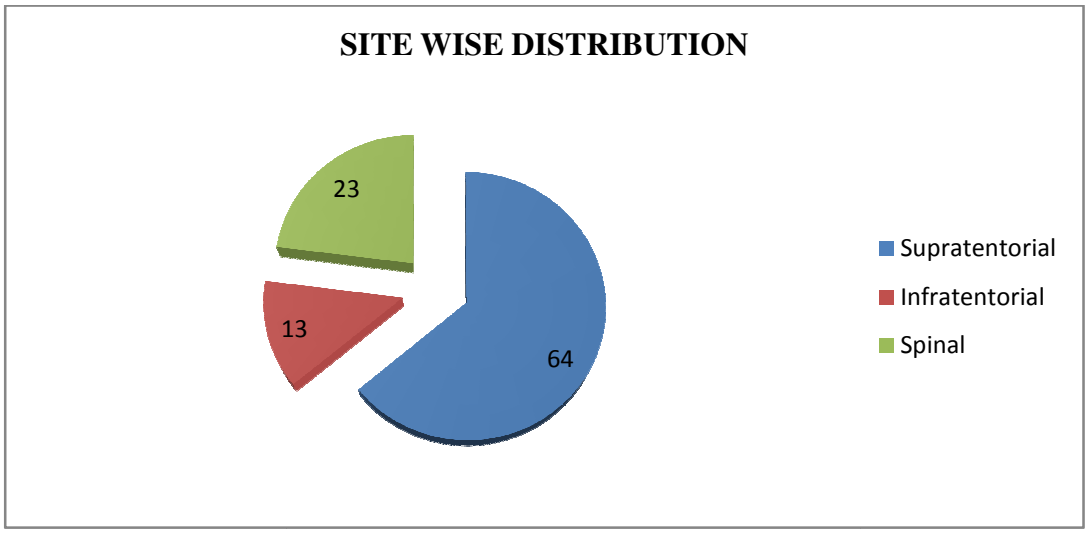
ANATOMICAL SITE WISE DISTRIBUTION OF MENINGIOMAS

LOCATION	CASES
Supratentorial	19(64%)
Infratentorial	4(13%)
Spinal	7(23%)

Among 30 cases studied ,19 cases were Supratentorial in location and 7 cases were Spinal (23%),and only 4 cases were Infratentorial in location in the present study.

CHART 3

ANATOMICAL SITE WISE DISTRIBUTION OF MENINGIOMAS



In the current study ,as depicted in the above Exploded Pie chart supratentorial location was the most common among other tumours followed by Spinal tumours constituting around 23% and Infratentorial tumours were least in location constituting only 13%.

TABLE 3

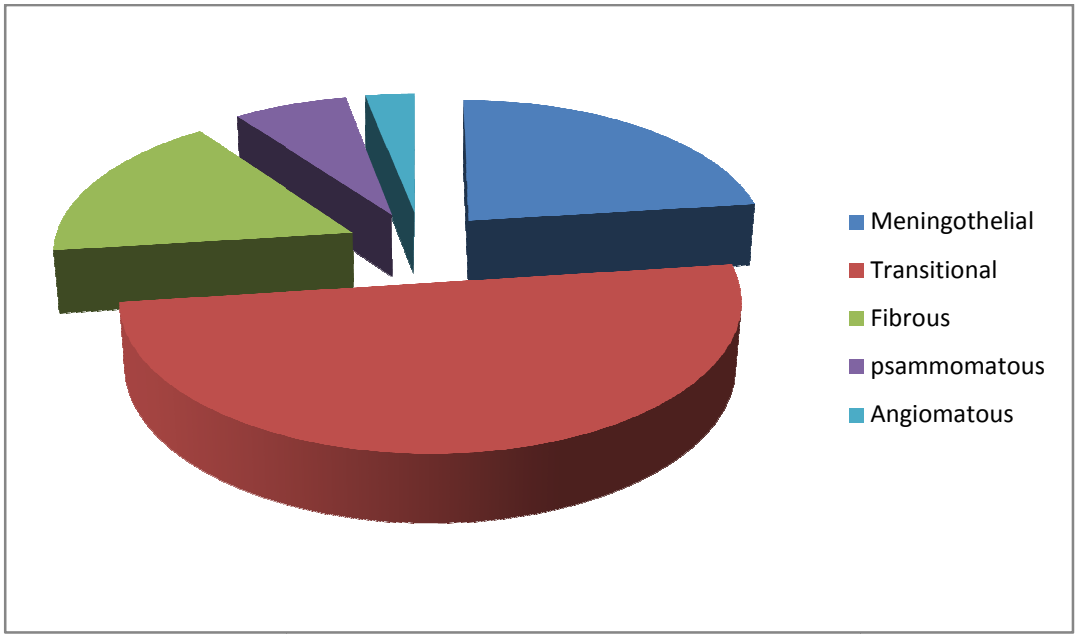
INCIDENCE OF VARIOUS SUBTYPES

SUBTYPE	PERCENTAGE IN THE STUDY
Meningothelial	23%
Transitional	50%
Fibrous	17%
Psammomatous	7%
Angiomatous	3%

In the present study among grade I tumours, which has 13 subtypes only five subtypes was observed commonly. Among the five subtypes, Transitional was the most commonly observed subtype constituting about 50 %,followed by Meningothelial which was around 23%,fibrous subtype (17%),Psammomatous type(7%),Angiomatous subtype.

CHART 4

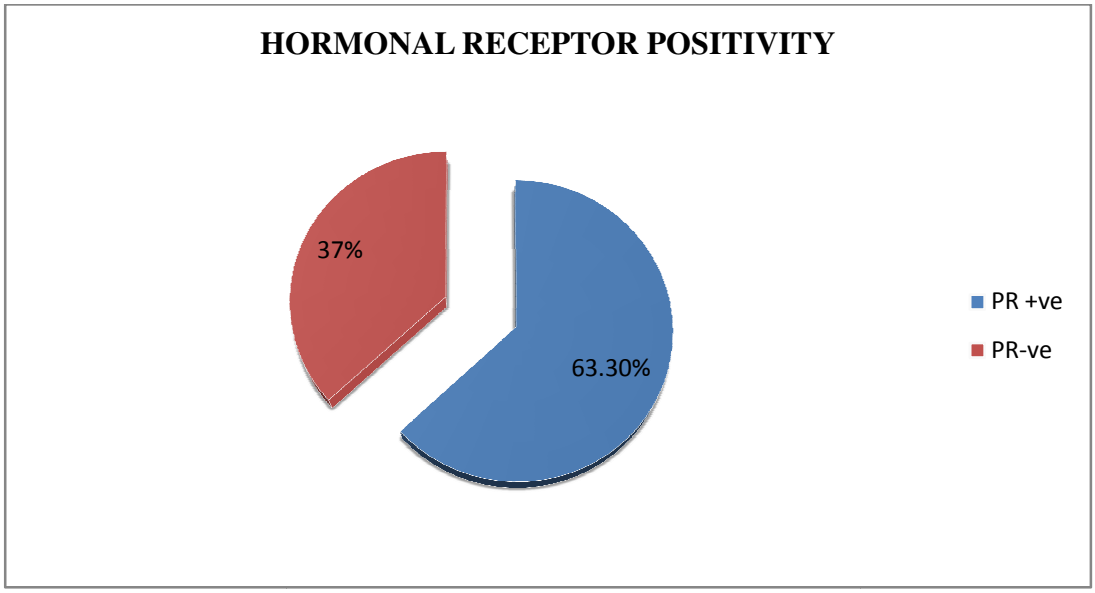
INCIDENCE OF VARIOUS SUBTYPES



As depicted in the above Pie chart, Transitional was most common subtype among others followed by other subtypes in decreasing order Meningothelial, Fibrous, Psammomatous, Angiomatous.

CHART 5

HORMONAL RECEPTOR STATUS IN MENINGIOMAS



HORMONAL RECEPTOR POSITIVITY:

TOTAL CASES:30

PROGESTERONE POSITIVE CASES: 19(63.3%)

PROGESTERONE NEGATIVE CASES:11(37%)

ESTROGEN RECEPTOR POSTIVITY:0(0%)

TABLE 4

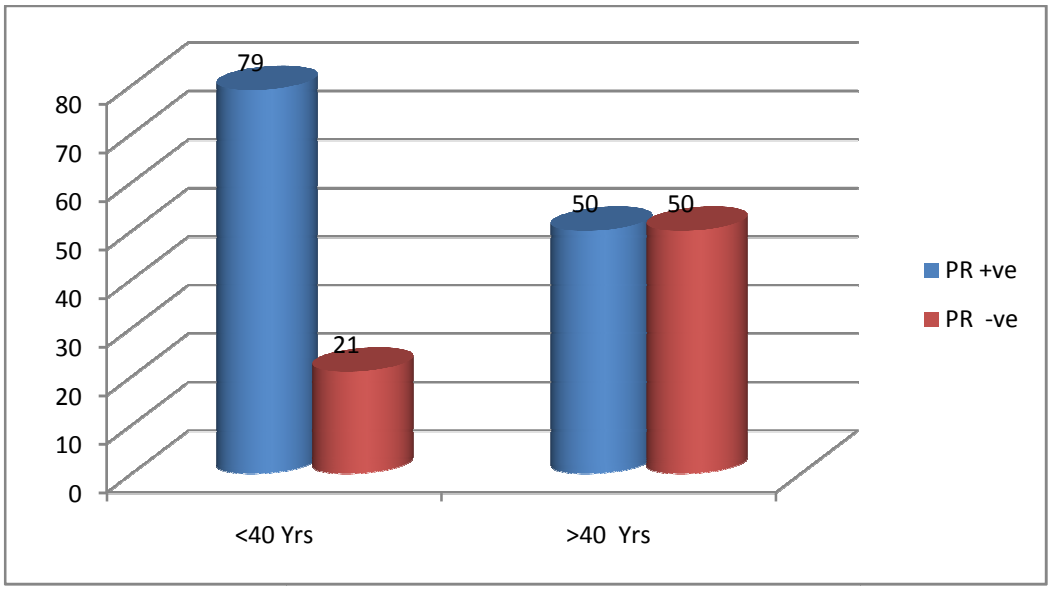
AGE WISE DISTRIBUTION OF PROGESTERONE RECEPTOR EXPRESSION

AGE	PR+VE	PR –VE
<40 YRS	11 (79%)	3 (21%)
>40YRS	8 (50%)	8 (50%)

In the current study out of 30 cases, 14 cases were seen in age group of < 40 yrs of which 11(79%) were PR positive and 3 (21%) were PR negative. Whereas out of the 16 cases which were > 40 yrs age group 8 (50%) were positive and 8(50%) were negative. These results were analysed using chi-square analysis and found to be statistically insignificant .(p=0.074)

CHART 6

AGE WISE DISTRIBUTION OF PROGESTERONE RECEPTOR EXPRESSION



In this clustered column diagram it is seen that PR positivity was higher in age group <40 years with 11(79%) out of 14 cases showing PR positivity than in age group >40 years which showed equal PR positive and PR negative cases. These results were analysed using chi-square analysis and found to be statistically insignificant.(p=0.074)

TABLE 5

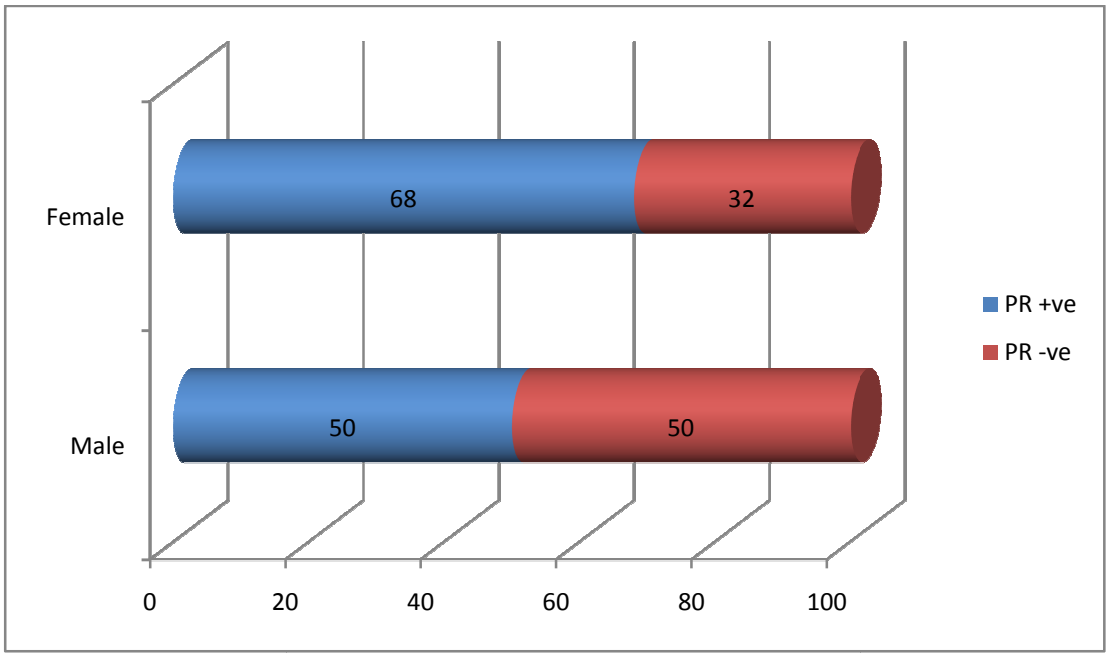
SEX WISE DISTRIBUTION OF PROGESTERONE RECEPTOR EXPRESSION

SEX	PR '+'ve (n)	PR '-' ve (n)
Male	4(50%)	4(50%)
Female	15(68%)	7(32%)

In the present study out of 22 females,15 cases (68%)were PR positive and 7 cases were PR negative. Whereas among 8 males PR positive and PR negative were 4 cases each that is 50% each. Chi-square analysis showed a p value of 0.03 which is statistically significant.

CHART 7

SEX WISEDISTRIBUTION OF PROGESTERONE RECEPTOR STATUS



In the present study as seen from this bar chart PR positivity was significantly higher in females about 68% than in males in which both PR positive and negative cases were 50 % each. These observations were statistically significant.($p<0.03$)

TABLE 6

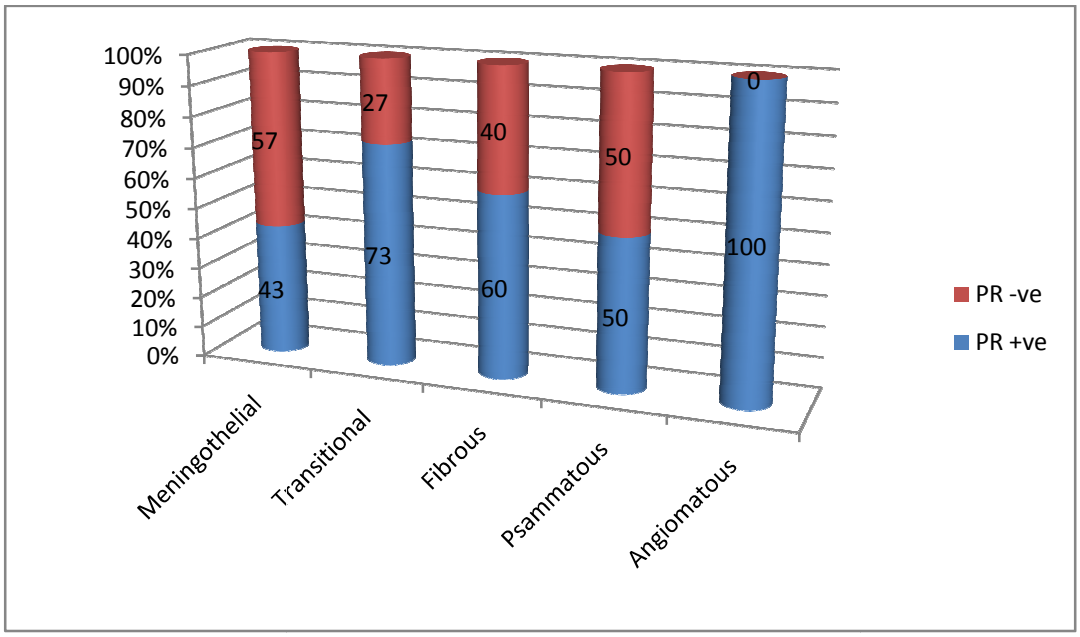
PR STATUS IN MENINGIOMA SUBTYPES

SUBTYPES	PR +ve	PR -ve
Meningothelial	43%	57%
Transitional	73%	27%
Fibrous	60%	40%
Psammatous	50%	50%
Angiomatous	100%	0%

As seen in the above table , PR positivity was 100 % in Angiomatous subtype followed by Transitional subtype showing 73% PR positive cases ,followed by Fibrous exhibiting 60% PR positivity. Psammomatous showed 50 % of PR positive and PR negative cases.PR positivity was least in Meningothelial subtype(43%).These results were statistically insignificant. .(p=15.7)

CHART 8

PROGESTERONE RECEPTOR STATUS AMONG MENINGIOMA SUBTYPES



In the present study as seen from the Bar chart, Angiomatous subtype showed 100% PR positivity and least PR positive subtype was Meningothelial subtype with only 43% cases showing Immunoreactivity for Progesterone receptor cases which is statistically insignificant.(p=15.7)

TABLE 7

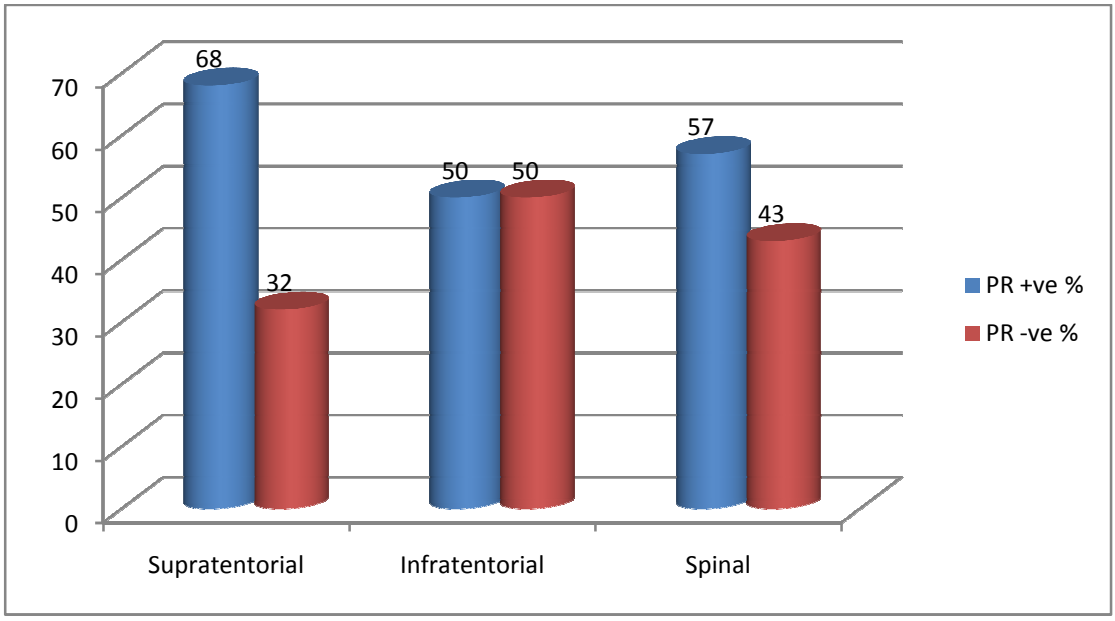
PROGESTERONE RECEPTOR EXPRESSION IN VARIOUS LOCATIONS

LOCATION	PR +ve	PR -ve
Supratentorial	13(68%)	6(32%)
Infratentorial	2(50%)	2(50%)
Spinal	4(57%)	3(43%)

From the above table PR positivity was higher in supratentorial tumours with 13 case(68%)s out of 19 cases, followed by spinal tumours with 4 out of 7 cases showed PR positivity. Infratentorial tumours showed equal PR positive and negative cases with 50 % each. Chi square analysis showed a statistically insignificant result .(p=0.67)

CHART 9

PROGESTERONE RECEPTOR EXPRESSION IN VARIOUS LOCATIONS



As depicted in the above Clustered cylinder column, PR immunoreactivity was expressed by 68% of supratentorial tumours, followed by spinal tumours with 57%.Infratentorial tumours showed equal PR positivity and PR negativity with 50% each. Chi square analysis showed a statistically insignificant result. (p=0.67)

TABLE 8

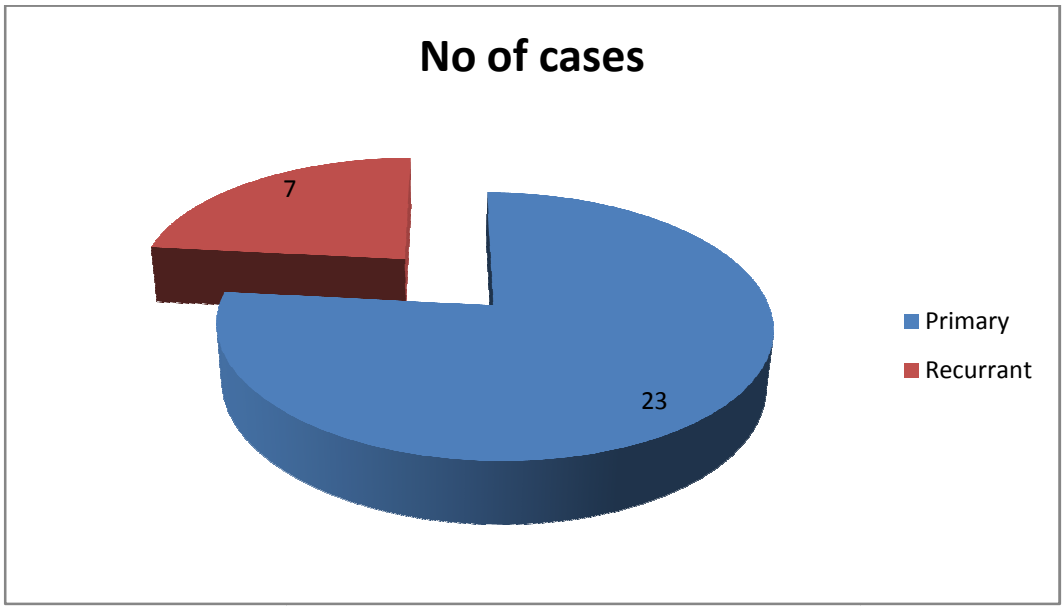
INCIDENCE OF RECURRENCE

CASES	NUMBER
Non recurrent	23
Recurrent	7
Total	30

In the present study total of 30 meningioma cases were studied, all of which were grade I tumours .Among grade 1 tumours ,recurrence was seen in 7 cases(23%) and 23 cases(77%) were non recurrent cases.

CHART 10

INCIDENCE OF RECURRENCE



As seen from the above Exploded 3-D pie chart Primary or non recurrent cases were around 77 % that is 23 cases, and recurrent cases were around 23% that is 7 cases.

TABLE 9

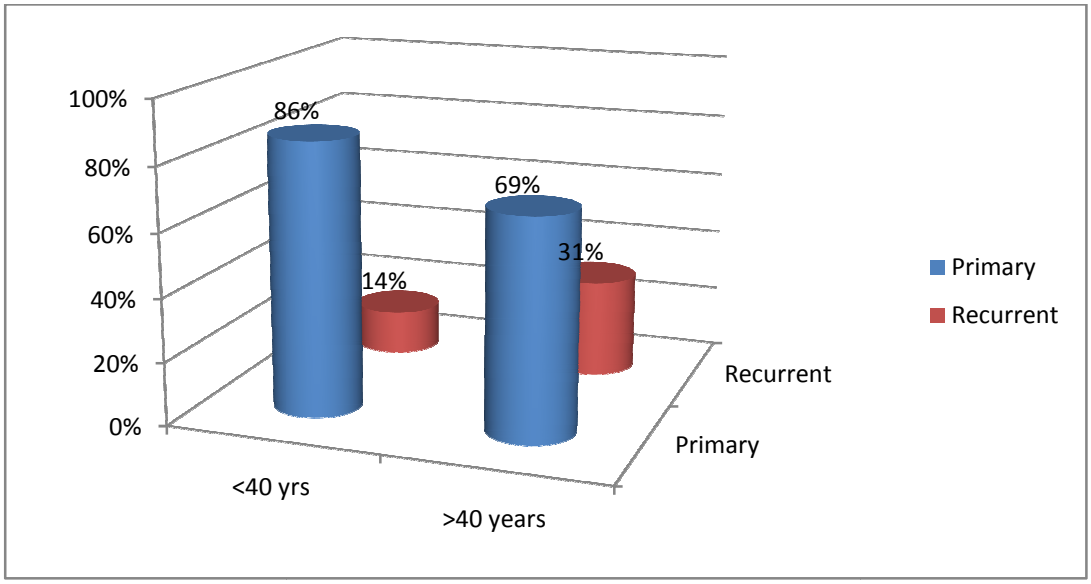
AGE DISTRIBUTION OF RECURRENT TUMOURS

AGE	NON RECURRENT	RECURRENT
<40 YRS	12(86%)	2(14%)
>40 YRS	11(69%)	5(31%)

Out of total 30 cases, 14 cases were <40 years, out of 14 cases only 2 cases showed recurrent tumour. Whereas out of 16 cases in age group >40 years,5 cases that is 31% showed recurrence. However recurrence was insignificantly related to age.(p=1.02)

CHART 11

AGE DISTRIBUTION OF RECURRENT TUMOURS



As noted in the above 3-D cylinder column chart, it is clear that recurrence was noted higher in age group >40 years with 5(31%) out of 16 cases showed recurrence, than in age group <40 years where only 2 out of 14 cases showed recurrence. However recurrence was insignificantly related to age.(p=1.02)

TABLE 10

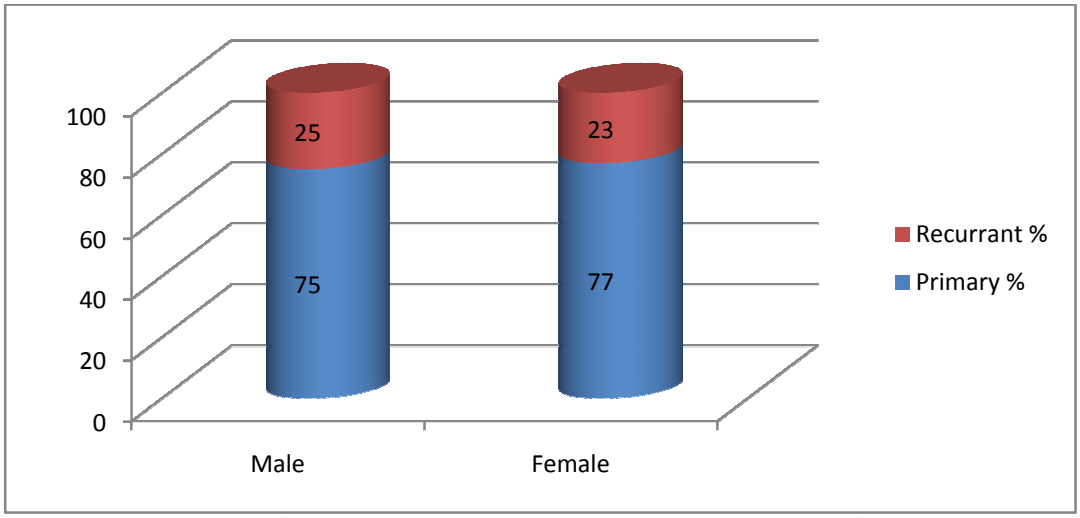
RECURRENT TUMOURS AND SEX DISTRIBUTION

Sex	Primary	Recurrent
Male	6(75%)	2(25%)
Female	17(77%)	5(23%)

In the present study, recurrent tumours were analysed with sex distribution . As noted from above table, recurrence was higher in males in which out of 8 males , 2 cases that is 25% showed recurrence whereas out of 22 cases of females, only 5 cases showed recurrence which constituted around 23%.Using chi-square test p value is 0.01 ,which is statistically significant

CHART 12

RECURRENT TUMOURS AND SEX DISTRIBUTION



As observed in the above stacked cylinder column chart, recurrence was slightly higher in males with 2(25%) out of 8 males showed recurrence compared to females which was only 23 %. Using chi-square test , p value is 0.01 ,which is statistically significant

TABLE 11

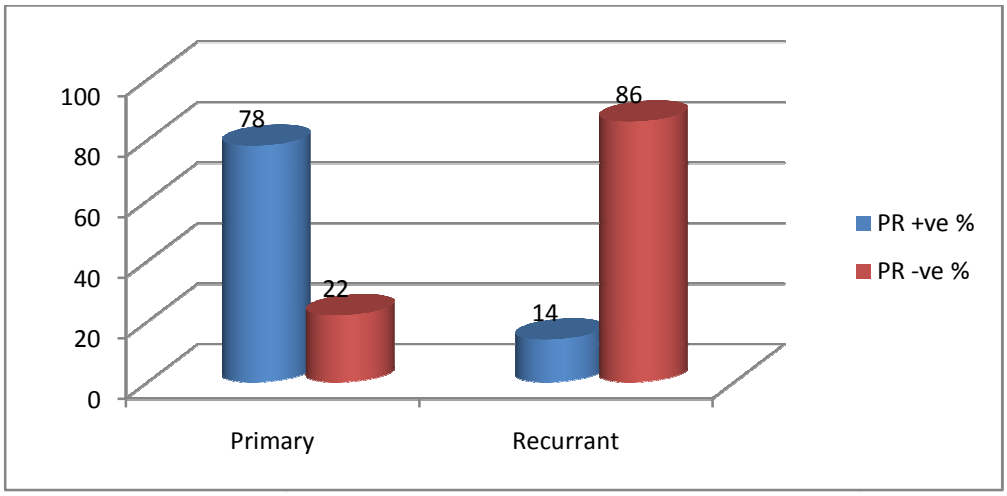
PROGESTERONE RECEPTOR STATUS IN NON RECURRENT VS RECURRENT TUMOURS

CASES	PR + ve	PR – ve
Non recurrent	18(78%)	5(22%)
Recurrent	1(14%)	6(86%)

As noted from the above table, Progesterone receptor immunoreactivity was analysed with non recurrent and recurrent tumours.PR positivity was expressed in higher percentage in non recurrent tumours than that of recurrent tumours. Out of total 23 primary cases, almost 18 cases (78%)showed PR positive immunoreactivity, Whereas among 7 recurrent cases only one case showed positive PR immunoreactivity. These results were statistically significant by chi-square analysis. (p=0.03)

CHART 13

PROGESTERONE RECEPTOR STATUS IN NON RECURRENT VS RECURRENT TUMOURS



In the current study, out of total 30 cases, PR positive immunoreactivity was significantly higher, that is nearly 18 cases(78%) showed PR positivity in non recurrent cases which was statistically significant and only 1 case(14%) was positive among recurrent cases. These results were statistically significant by chi-square analysis. (p=0.03)

TABLE 12

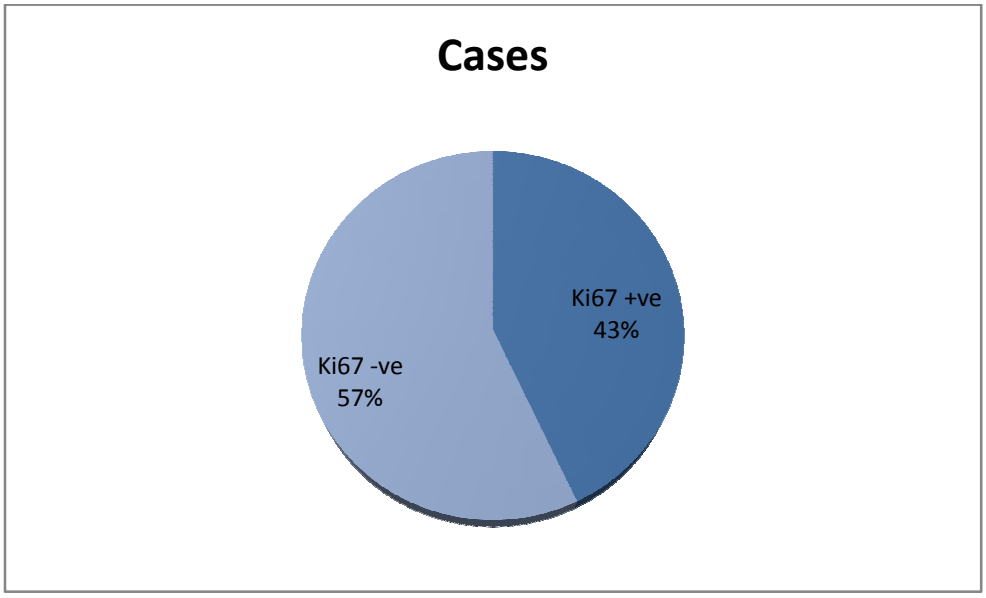
Ki67 EXPRESSION IN MENINGIOMAS

MARKER	CASES
Ki67 +ve	13(43%)
Ki67 -ve	17(57%)

In the current study,Ki67 a proliferative marker, is expressed in 13 out of 30 cases and the remaining 17 cases (57%) were negative. It is clear from the above table that Ki67 negative cases were in higher percentage in grade I meningioma than Ki67 positive cases.

CHART 14

Ki67 EXPRESSION IN MENINGIOMAS



As shown in the above pie chart, Ki67 negative cases were significantly higher than Ki67 positive cases. Out of total 30 cases observed in the current study, 17 cases did not exhibit Ki67 immunoreactivity and remaining 13 cases was Ki67 positive.

TABLE 13

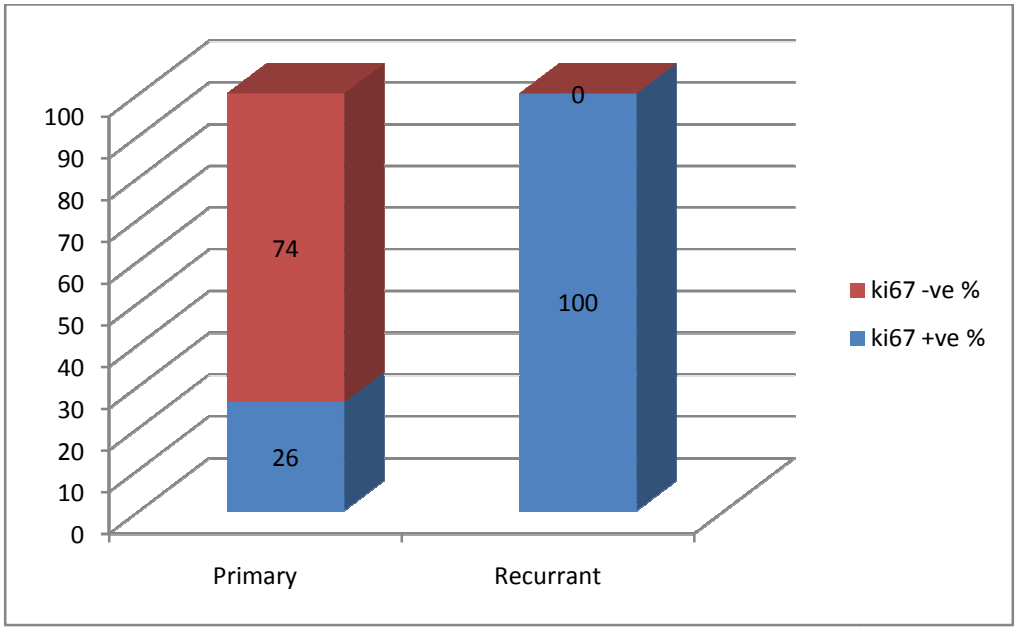
Ki67 STATUS AND RECURRENCE

CASES	Ki67 +ve	Ki67 –ve %
Non recurrent	6(26%)	17(74)%)
Recurrent	7(100%)	0(0%)

In the present study, Ki67 immunoreactivity was analysed in non recurrent and recurrent cases . All the 7 recurrent cases were Ki67 positive. Whereas only 6 cases out of 23 of non recurrent cases were Ki67 positive. These results were statistically significant by chi square analysis. (p value <0.001)

CHART 15

Ki67 STATUS AND RECURRENCE:



As depicted in the above clustered cylinder column chart, it is clear that all the 7 recurrent cases showed Ki67 positivity which was statistically significant. Whereas out of 23 non recurrent cases only 6 cases showed Ki67 positivity. These results were analysed using Chi-square test which is statistically significant . (p value <0.001)

TABLE 14

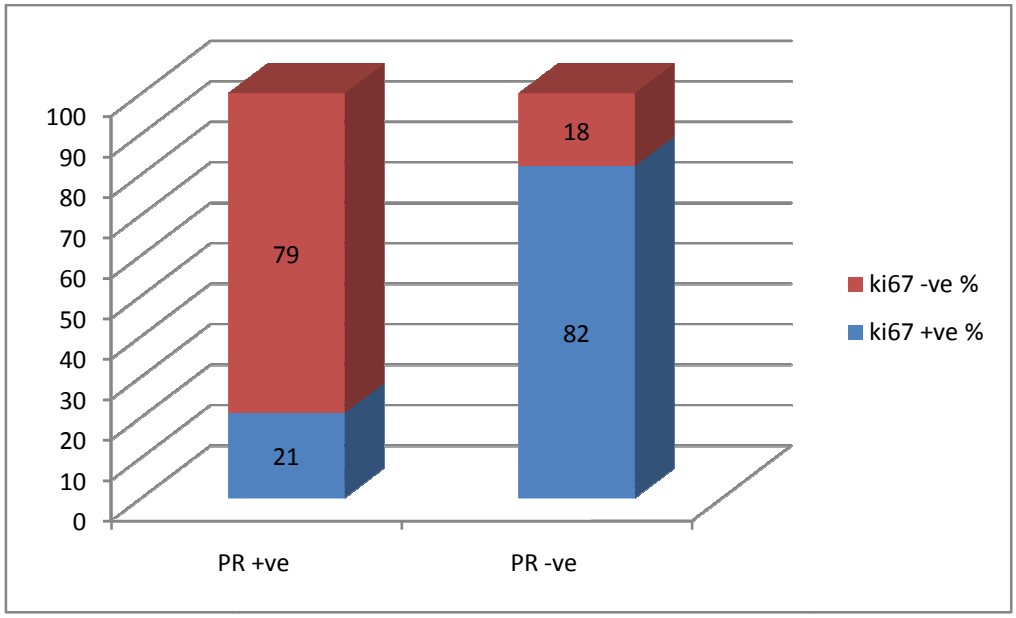
CORRELATION OF PROGESTERONE RECEPTOR AND Ki67 EXPRESSION

MARKER	Ki67 +ve	Ki67 –ve
PR +ve	4(21%)	15(79%)
PR –ve	9(82%)	2(18%)

In the present study, PR immunoreactivity was compared with Ki67 expression. From the above table an inverse relationship was observed between PR and Ki67 expression. That is out of 19 PR positive cases ,almost 15 cases were Ki67 negative whereas out of 11 PR negative cases , Ki67 was positive in 9 cases. Chi-square analysis showed a statistically significant result. $p<0.003$

CHART 16

CORRELATION OF PROGESTERONE RECEPTOR AND Ki67 EXPRESSION



From the above clustered cylinder column chart, an inverse relationship was observed between PR and ki67 expression. That is out of 19 PR positive cases , almost 15 cases were Ki67 negative whereas out of 11 PR negative cases , Ki67 was positive in 9 cases. Chi-square analysis showed a statistically significant result (.p<0.003)

COLOUR PLATES

HISTOPATHOLOGICAL HALLMARKS OF MENINGIOMA

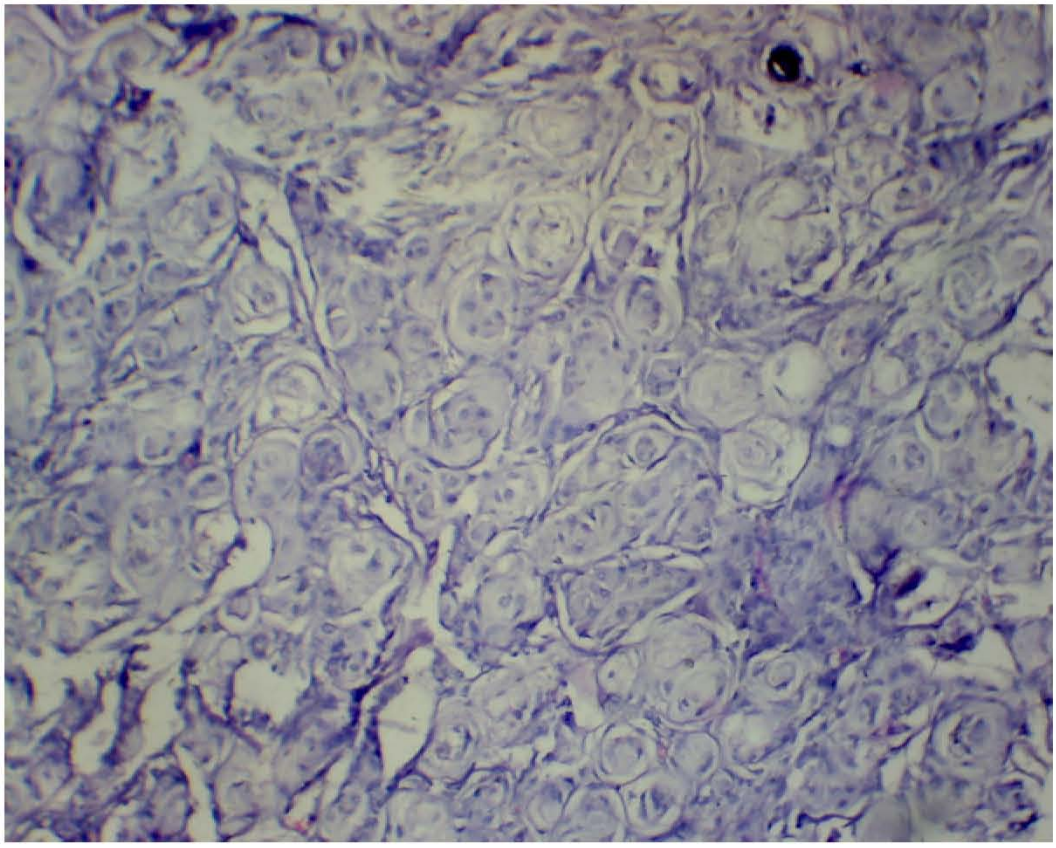


Fig 1. Meningioma – Whorls and Psammoma Body -H&E(10x)

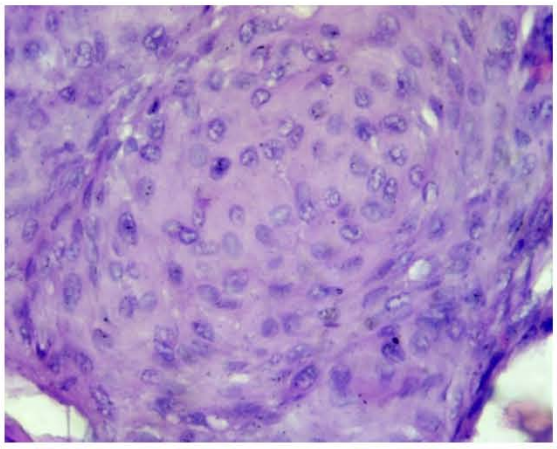


Fig 2. Meningeal Whorls (40X)

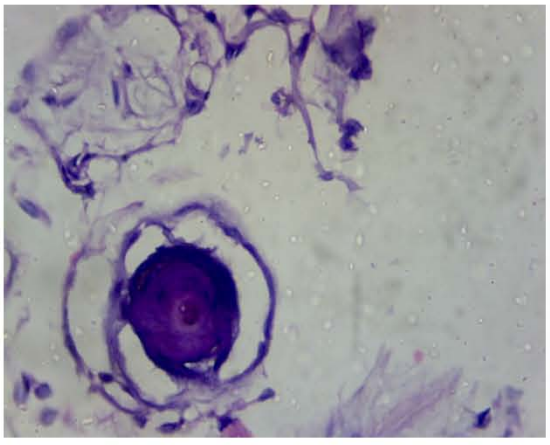


Fig 3.Psammoma Body(40X)

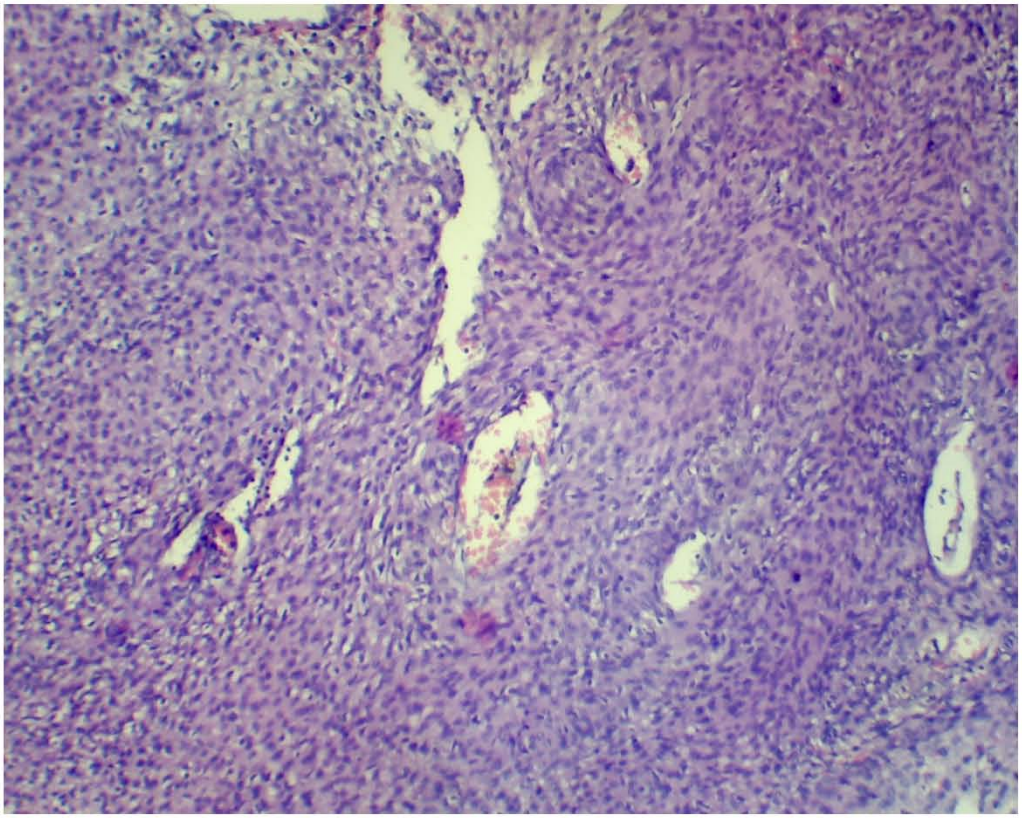


Fig 4.Transitional Meningioma – H & E (10X)

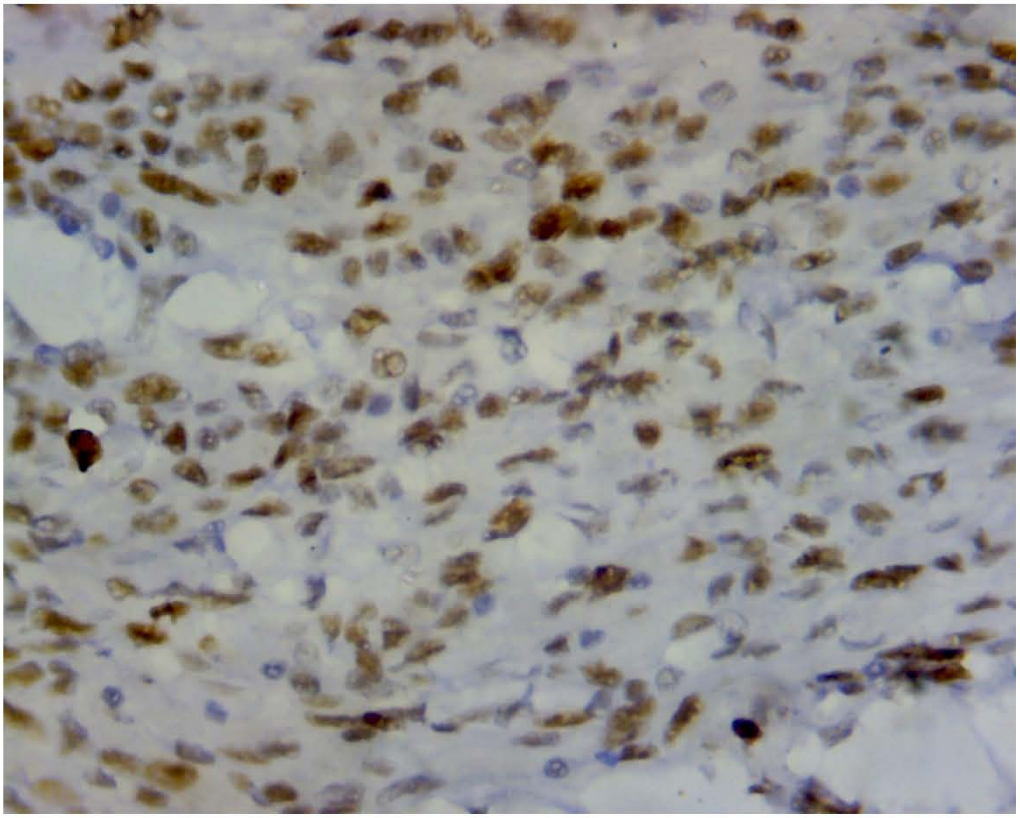


Fig 5. Transitional Meningioma Showing Progesterone Receptor Nuclear Positivity (40X)

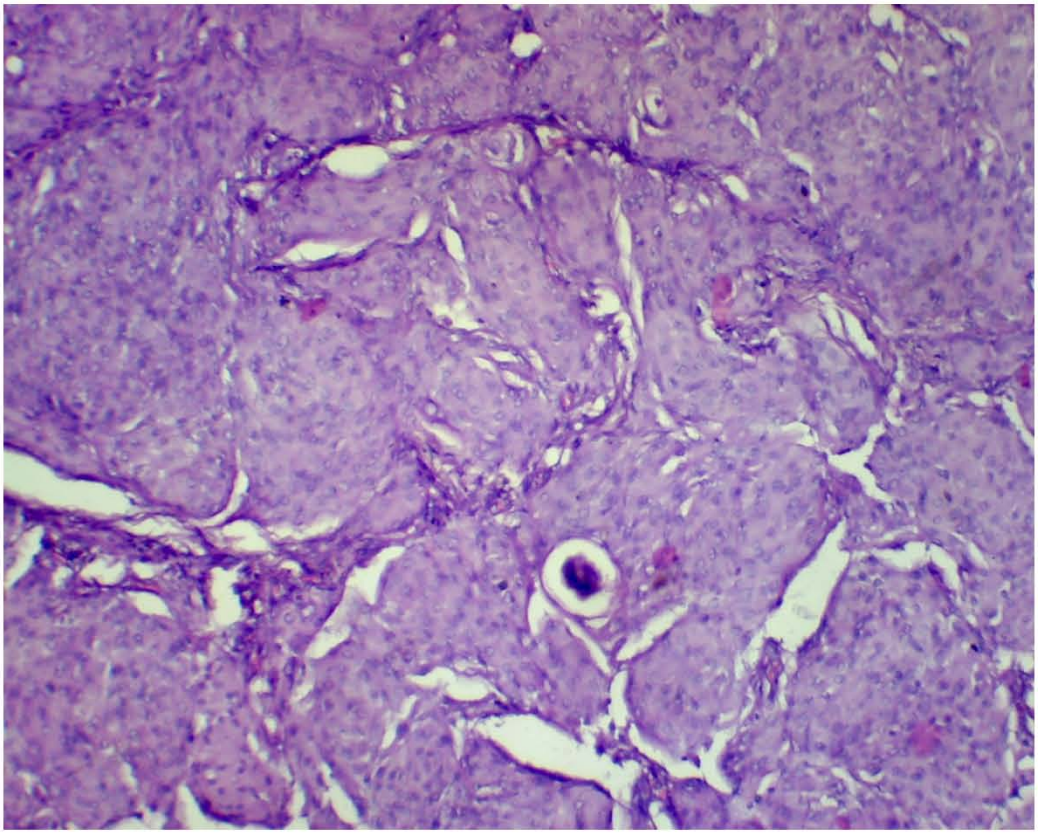


Fig 6.Meningothelial Meningioma H & E (10X)

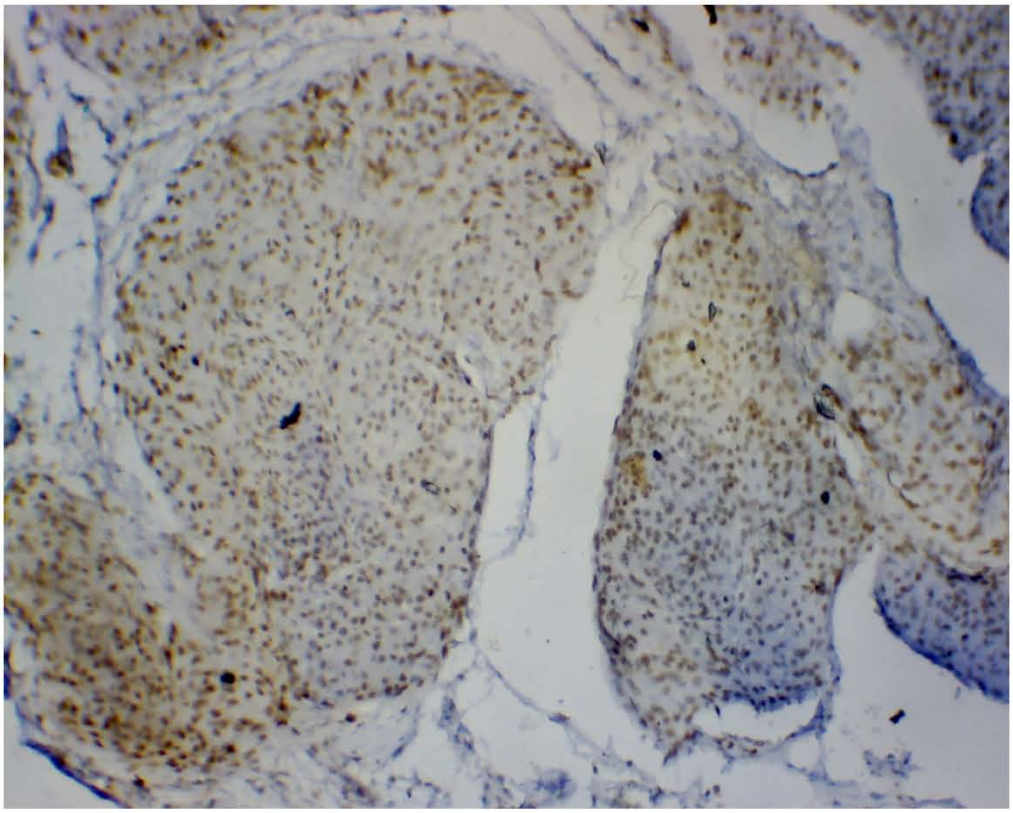


Fig 7.Meningothelial Meningioma Showing Progesterone Receptor Nuclear Positivity (10X)

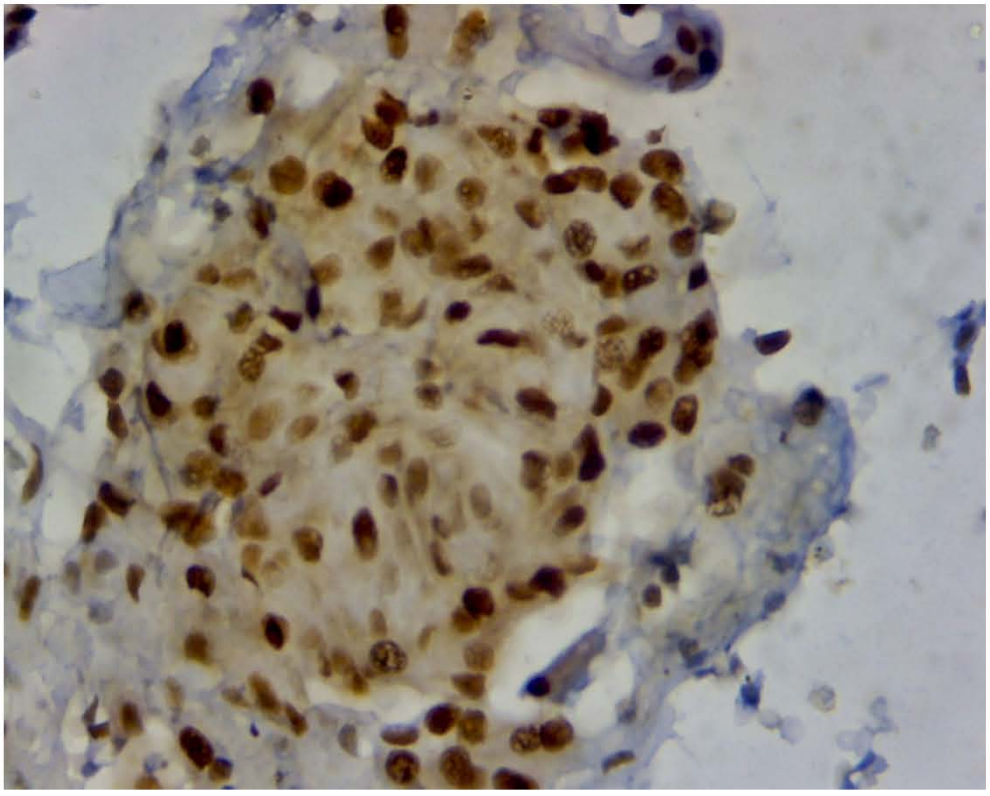


Fig 8.Meningothelial Meningioma Showing Progesterone Receptor Nuclear Positivity (40X)

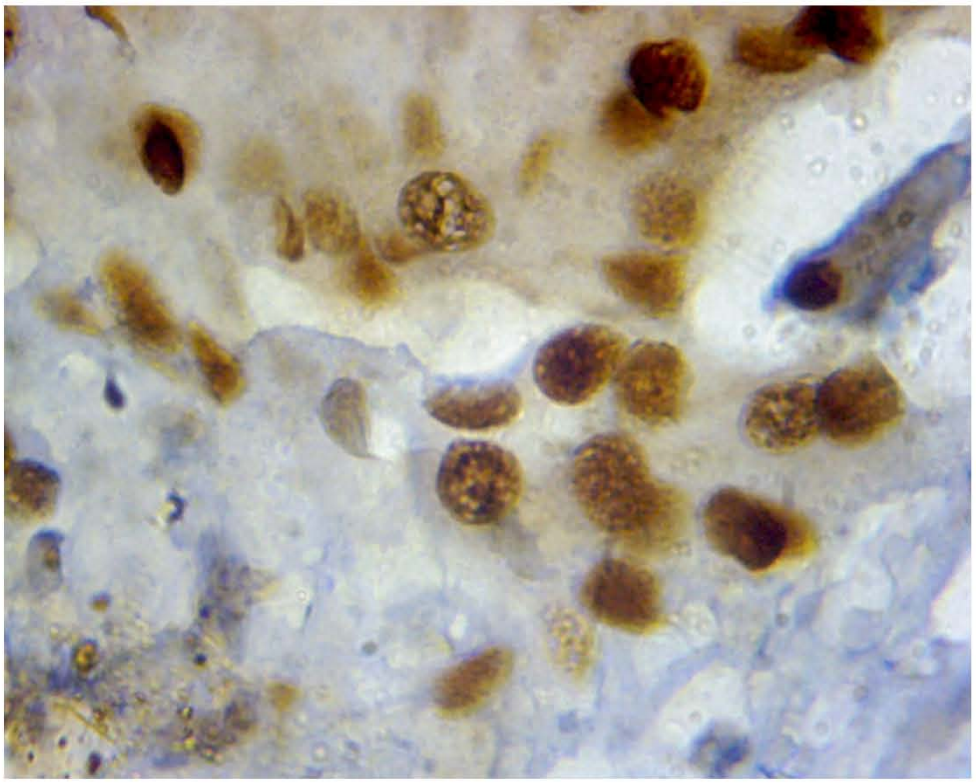


Fig 9.Meningothelial Meningioma Showing Progesterone Receptor Nuclear Positivity (100X)

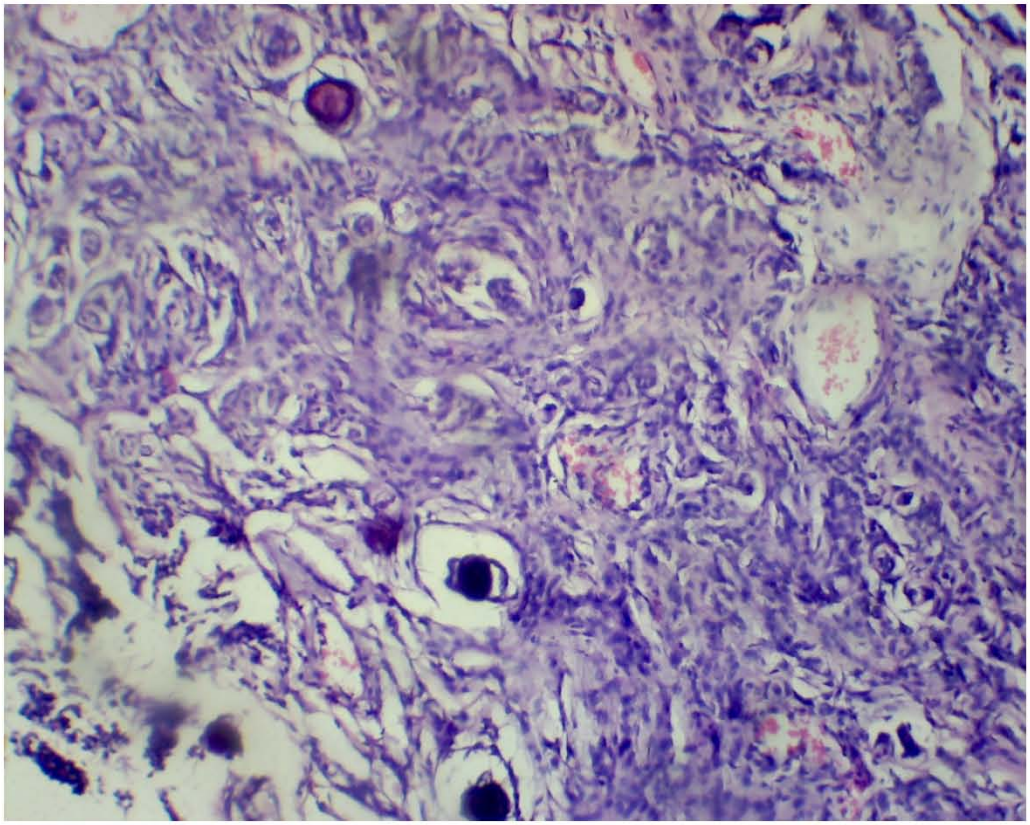


Fig.10-Psammomatous Meningioma – H & E (10X)

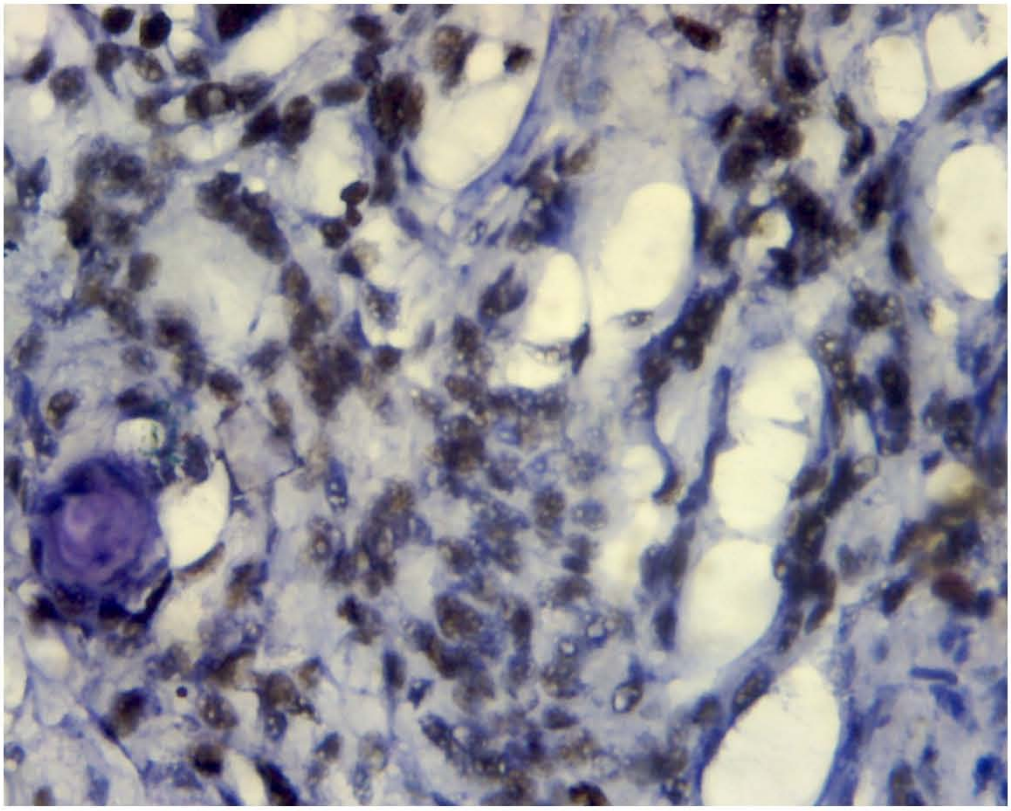


Fig.11-Psammomatous Meningioma Showing Ki67 Nuclear Positivity (40X)

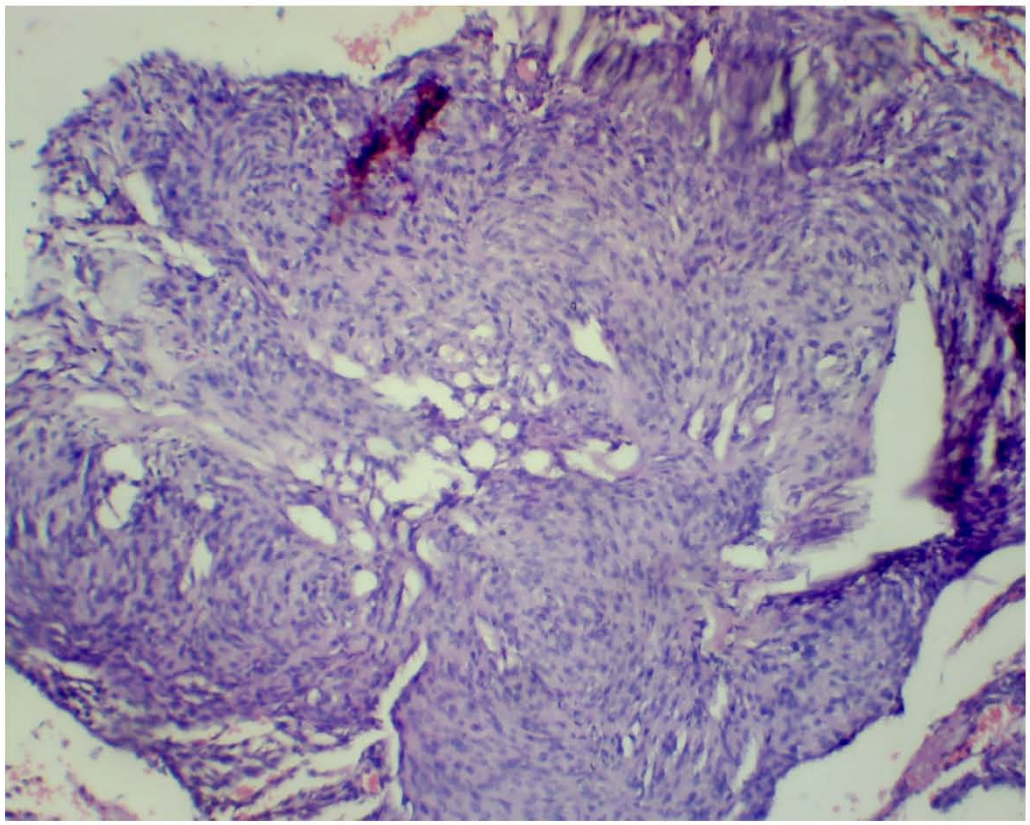


Fig.12-Fibrous Meningioma – H & E (10X)

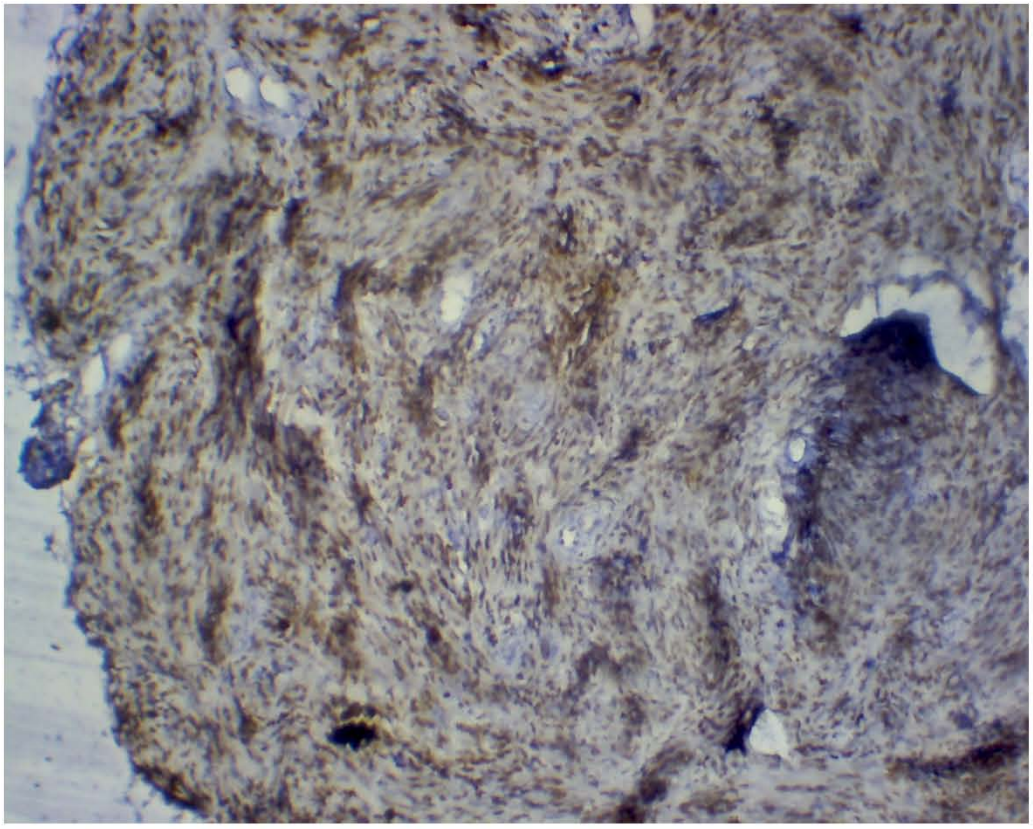


Fig.13-Fibrous Meningioma – Ki67 Nuclear Positivity(10X)

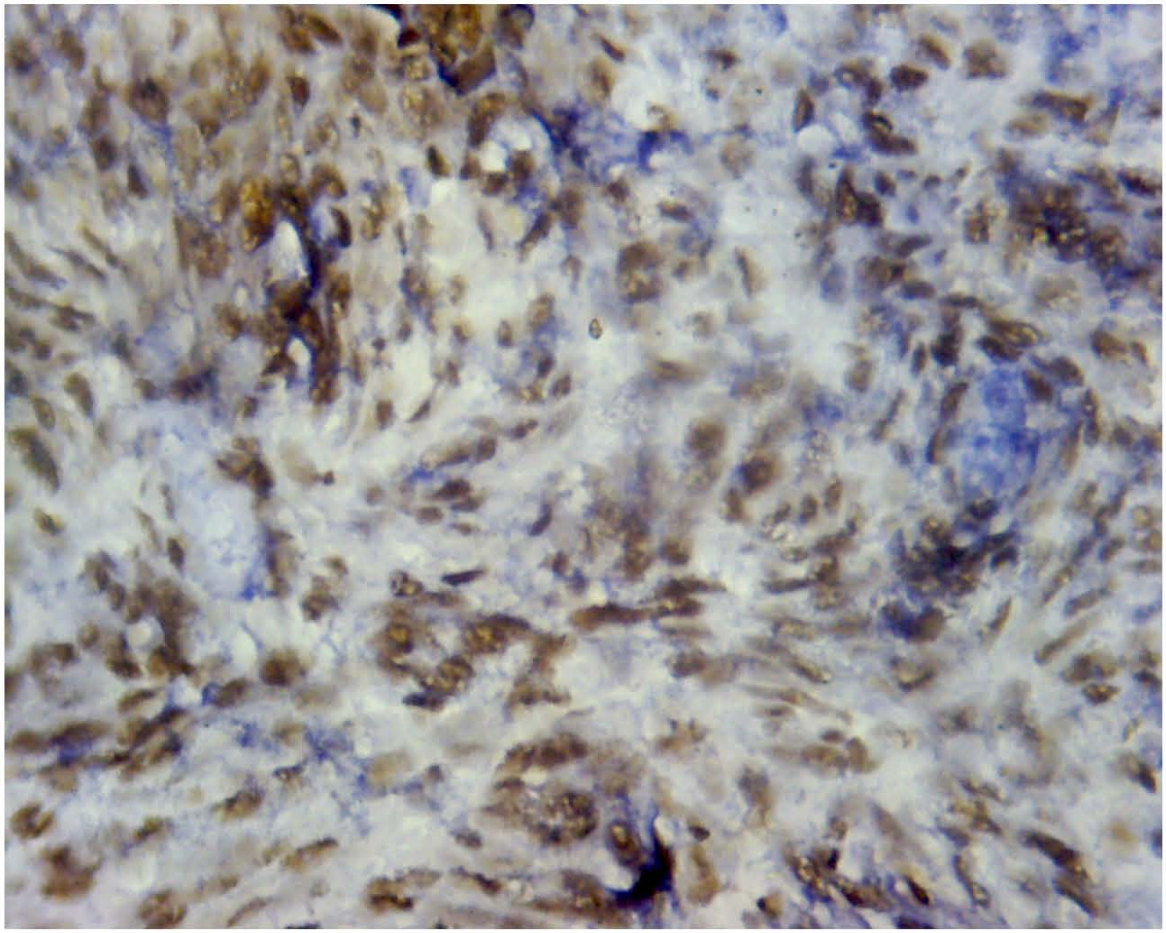


Fig.14- Fibrous Meningioma – Ki67 Nuclear Positivity(40X)

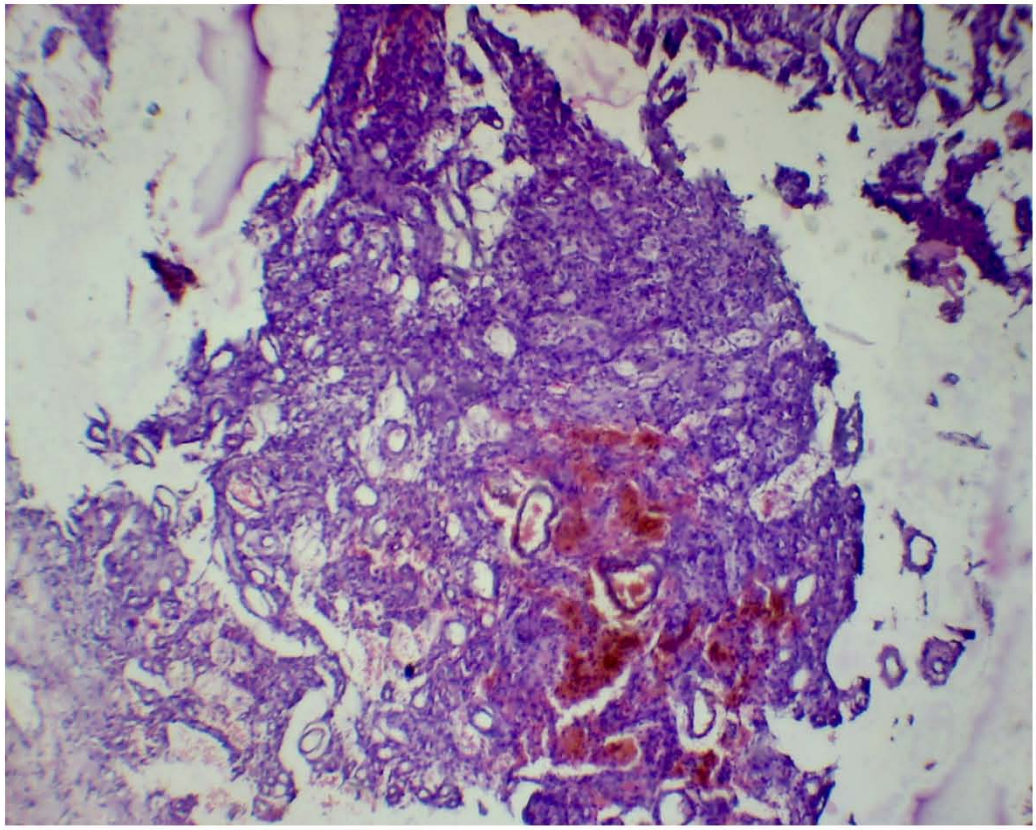


Fig 15-Meningioma – Angiomatous Subtype - H & E (4X)

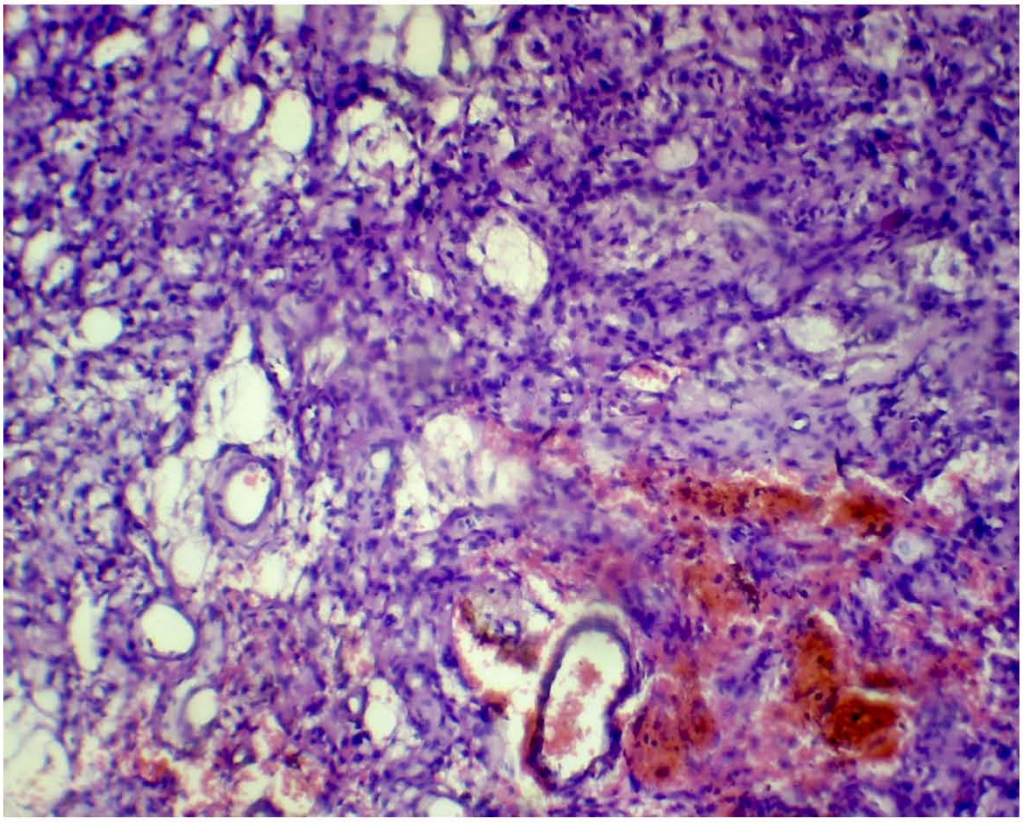


Fig.16-Meningioma – Angiomatous Subtype - H & E (10X)

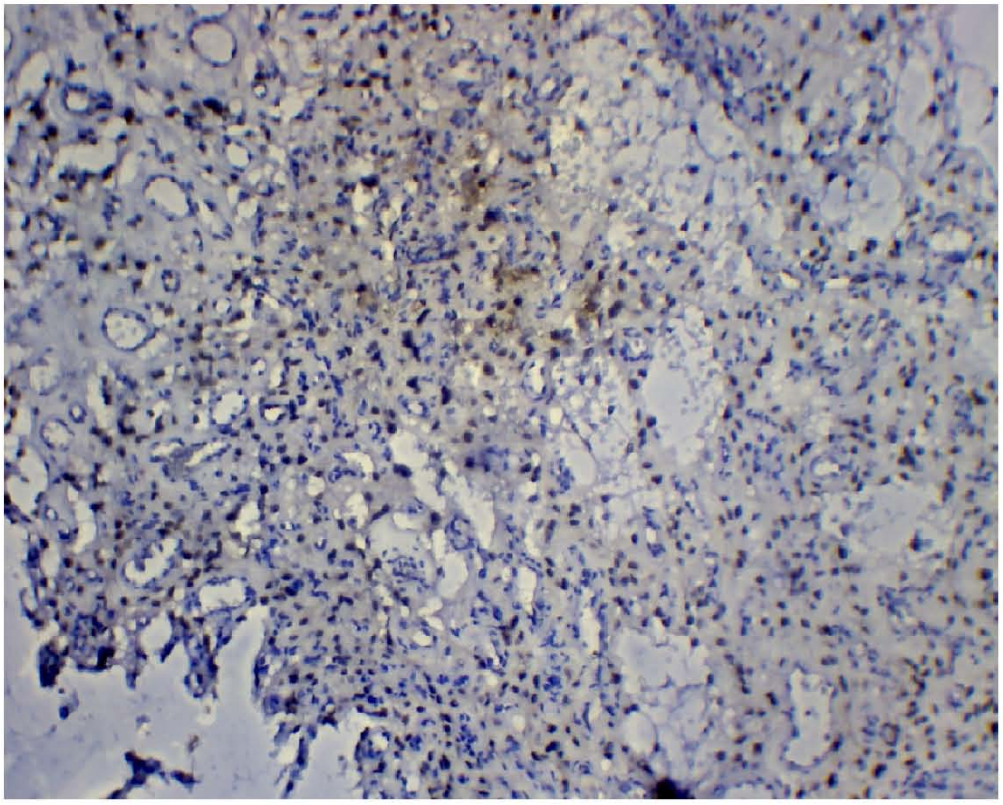


Fig.17–Angiomatous meningioma showing Progesterone receptor nuclear positivity(10X)

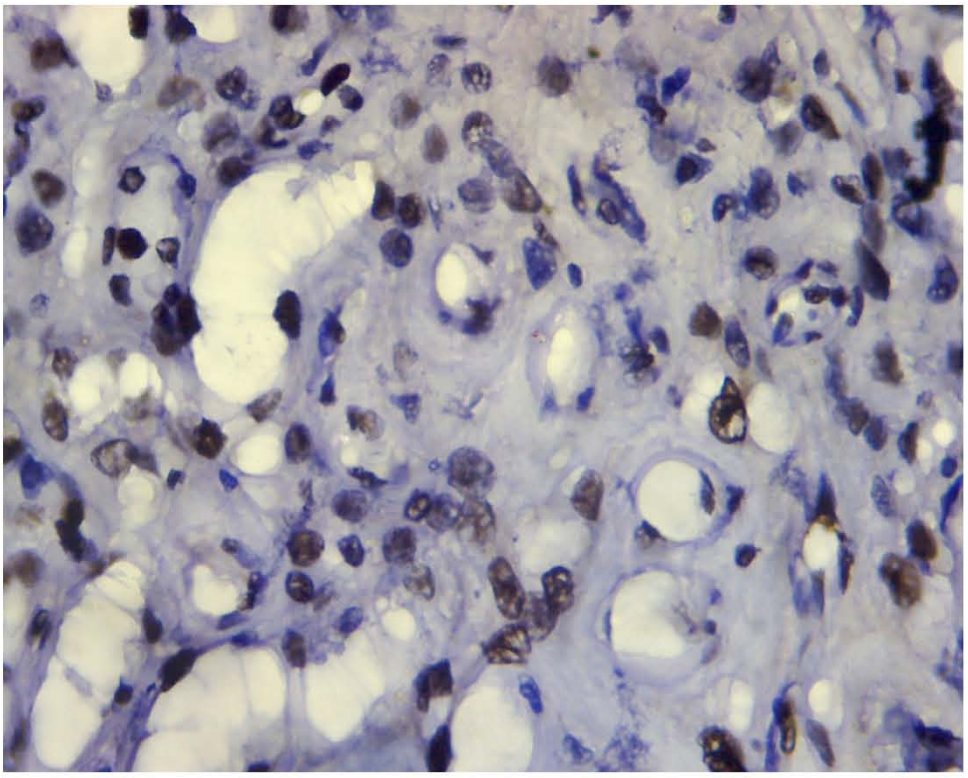


Fig.18- Angiomatous Meningioma showing Progesterone Receptor Nuclear Positivity(40X)

DISCUSSION

DISCUSSION

Meningiomas constitute the single largest group of tumour arising from the meningothelial cells. It can range from benign meningioma (WHO grade I) to atypical and anaplastic meningioma (WHO grade II and grade III) respectively. Meningioma constitute about 13-26% of primary intracranial tumours. The annual incidence rate of meningioma is about 6 per 100000 population. Of these benign meningiomas constitute the majority of cases followed by atypical and anaplastic meningioma. Yet benign grade I meningiomas have an increased tendency to recur.[38] Eventhough tumour grade and subtype are strong prognostic factors ,benign biologically aggressive meningiomas cannot be identified by routine histology alone. Hence the need for identification of newer prognostic indicators arises ,to predict the clinical behaviour. Various literature have shown that detection of progesterone receptor and proliferative index Ki67 might predict the clinical behaviour of meningioma and patient survival.

In the present study three factors that is progesterone receptor, Estrogen receptor expression, proliferation indices were studied in the meningioma specimens and their possible correlation were analysed demographically, histomorphologically and by immunohistochemistry.

Thirty cases with meningioma were included in the study. The age of patients ranges from 27 – 75 years. Mean age was 45 .7 +/- 13.1 years. (TABLE 1).This is in accordance with the results by El-Badawy et al (2013) in which mean age was 46.7 years. [43]Similar studies conducted by Ashraf Fakhrjou et al (2012),and in Chennai by Shalinee Rao et al(2009)showed mean age was 52.9 years.[44],[45] Also a study by Roser et al(2004) in which 505 meningiomas specimens was examined , the mean age of PR positivity was 55.4 years .[46]

Out of 30 cases studied , females were 22 in number outnumbering males who were 8 in number(.i.e)Females constituted around 73.3% and males were 27%.The female: male ratio is 2.7:1.(TABLE 2).This is similar to the study by Ashraf Fakhrjou et al (2012) in which out of 50 cases, Females were 76.5%(n=26),males were 23.5 %(n=8)[44]. Al-Nuaimy et a (2012) studied 50 meningioma cases in which females (n=34) outnumbered males (n=16).[47] Shalinee Rao et al (2009) similarly showed a increased female: male ratio with 1.4:1[45].Nasirin Shayanfar et al (2009) studied 78 cases in which F:M ratio was 2.5:1[48].Similar studies by Taghipur et al (2007) showed out of 51 cases ,21cases were females with males constituting only 20 cases[49] and study by Sndan Milenkovie et al (2004) also showed a female preponderance .[50]

Incidence of various subtypes is as follows.

	Transitional (%)	**Meningothelial (%)**	**Fibrous (%)**	**Angio-matous (%)**	**Psammo-matous (%)**
Current study	50	23	17	13	7
Milenkovie et al., 2004	10	26.6	40	6.6	6.6
Shayanfar et al., 2009	36	40	24	-	-

The study includes the following subtypes of meningiomas, Transitional type, Meningothelial type, Fibrous type, Angiomatous and Psammomatous subtypes. Of these transitional meningioma found to be the most common subtype ,constitutes about 50%,which is followed by meningothelial subtype which constitutes around 23%.The other subtypes were fibrous ,angiomatous, and psammomatous which constitutes around 17%,13%and 7% respectively. (TABLE 3) A study by Shayanfar et al., 2009 showed Meningothelial subtype to be the most common of all constituting around 40% followed by transitional and fibrous constituting about 36% and 24 % respectively. [(48)]These values in the present study were approximately same as in these studies. A study by Al-Nuaimy et al (2009) also showed a similar result with 57% of meningothelial cases.[(47)]

Out of total thirty cases studied nineteen cases were PR positive and eleven cases were PR negative which constitutes 63% and 37% respectively. None of the thirty cases showed immunoreactivity to Estrogen receptor .(CHART 5). Similarly the expression of PR in various other studies are as follows. According to Al-Nuaimy et al., 2012 PR positivity was present in 72% of cases with 28% negative. [47] In a study by Shayanfar et al., 2009 the PR positivity was 96.8% [48], in another study by Taghipur et al., 2009 the PR positivity was noted in 68.6% of cases[49] and a study by Milenkovie et al., 2004 out of 30 cases PR positivity was present in 57% of cases.[50] In all above studies ER was not expressed in any of the case. Thus comparing all the above studies there is a consistent expression of PR positivity of more than 50%, and ER was 0% Thus our study correlates well with all the above studies.

PR positivity was analysed with the age of the patients. Of total 30 cases , patients with age less than 40 years were 14 in number which constituted around 46.6% and patients with age equal to or more than 40 years, were 16 in number which constituted about 53.3%.Fourteen cases with age less than 40 years, PR positivity was observed in 11 cases(78.5%) and 3 cases(50%) were PR negative . Out of 16 cases with age equal to or more than 40 years PR positive and negative were equal. In short PR positivity was observed higher in patients of less than 40

years (TABLE 4).These results were analysed by chi-square analysis and p value was 0.074.Hence PR was insignificantly related to age. However a study by Al-Nuaimy et al ,in 2012, PR was positive in age group of 41-50 years which is slightly higher in age compared to the present study[47].Also Roser et al (2004) showed mean age of PR positivity to be 55.4 years for females and 51.5 years for males.[46]

PR positivity was analysed with sex of the patients. Of the total 30 cases, 22 were females and 8 were males. Out of 22 females, PR positive immunoreactivity was observed in 15 cases which constituted around 68% and the remaining 7 cases were PR negative which is 37%.Of the 8 males studied PR positive and negative cases were equal ,50% each.(TABLE 5)In a similar study by Al-Nuaimy et al.,2012 PR was expressed in 72% of females and 20% of males.[47] Another study by Taghipour et al., 2007, 80% of female cases showed PR positivity similarly 67.5% of females cases showed PR positivity (Veherjein et al.,2001).[49]

Percentage of PR positivity in various subtypes mentioned below:

(TABLE 6)

	Mening-othelial	**Transitional**	**Fibrous**	**Psammo-matous**	**Angio-matous**
Current study	43%	73%	60%	50%	100%
El-Badawy et al., 2013	100%	50%	33.3%	-	-
Al-Nuaimy et al., 2012	83%	75%	100%	-	66.6%
Omulecka et al., 2006	100%	95%	46%	-	-
Roser et al., 2004	64.6%	50%	31%	60%	66.6%

Grade I meningioma subtypes observed in the present study were Transitional, Meningothelial, Fibrous,Angiomatous,Psammomatous. PR status was analysed with the various subtypes observed in our study. PR positivity was expressed by 100% of angiomatous subtype followed by Transitional type which showed 73% PR positivity .The other subtypes with PR positivity in decreasing order is as follows-Fibrous, Psammomatous, Meningothelial with 60 %,50%,43% respectively. These results were analysed using Chi-square test which showed a p value of 15.7.Hence PR expression was insignificantly related to meningioma

subtypes. Various other studies show a differing results.A study El-Badawy et al., 2013 in which meningothelial showed 100 % PR expression followed by Transitional 50%, fibrous 33.3% [43].Another study by Al-Nuaimy et al 2012,showed a contrasting result in which PR positivity was 100% in fibrous subtype followed by the below mentioned subtypes in decreasing order –meningothelial 83%, Transitional 75%,Angiomatous type 66.6%.Roser et al in 2004 showed angiomatous subtype with maximum PR expression constituting about 66.6% followed by meningothelial 64.6%,psammomatous 60 %,transitional 50% and fibrous 31.1% [47].A study by Omulecka et al 2004,showed a 100 % PR positivity in Meningothelial subtype followed by transitional 95%,fibrous 46 % [51].These differing results could be explained by the various stem cell factors involved in the Progesterone receptor expression in meningiomas.

Correlation of site of occurance and PR positivity (TABLE 7)

In the present study, out of 30 cases ,19 cases were supratentorial in location,7 cases were spinal,4 were infratentorial in location. Of the total 19 supratentorial cases, positive PR immunoreactivity was observed in 13 cases which consititued about 68.42%.Of the 7 spinal cases 4 were PR positive which were around 57%. Infratentorial tumours showed equal PR positive and PR negative cases with 50% in each group.Thus PR

positivity was higher in supratentorial tumours than in spinal and infratentorial tumours.However Chi-square analysis showed a statistically insignificant relation between PR expression and location of tumour. ($p>0.05$) .These results were similar to other study by Milenkovie et al (2004) in which no statistically significant correlation was obtained between PR expression and location of the tumour. [51]

From the thirty meningioma cases included in the study, incidence of recurrence was analysed. Criteria for recurrence is, Known case of meningioma, (i.e) previously diagnosed and proved as meningioma by histopathology, now again presenting with clinical, and radiological signs of meningioma and proved as meningioma by histopathology , was taken as recurrence. Of the 30 cases ,recurrence was seen in 7 cases and non recurrent cases were 23 in number.(i.e)recurrent cases constituted around 23% and recurrent cases was77% (TABLE 8).These results were in accordance with a study by El-Badawy et al., 2013 ,in which out of 30 meningioma cases, non recurrent and recurrent cases were equal constituting 50 % each, [43] and also a study by Al-Nuaimy et al (2012),where a total of 50 cases were studied in which non-recurrent cases were around 86% and recurrent cases constituted around 14%, [47] and also a study by Vranic 2010,where out of 54 cases studied, non

recurrent cases were 35 in number and recurrent cases were 19 in number.[35]

In the present study, age distribution of recurrent tumours were analysed. Cases <40 years who presented with recurrence were around 14.2% (n=2)and patients >40 years with recurrence were 31.2%(n=5) (TABLE 8)

Similar results were seen in studies by El-Badawy et al (2013),Al-Nuiamy et al (2012) no correlation was observed between recurrence and age of the patients.[43,47]

In the present study, sex wise distribution of recurrent tumours were analysed.2 out of 8 males show recurrence which constitutes 25%, in contrast only 5 out of 22 females (23%) show recurrence (TABLE 10).These results were analysed using chi-square analysis which is statistically significant with p value of 0.01.This is similar to study by El-Badawy et al (2013)[43] which showed recurrence to be more common in males than females,and a study by Al-Nuaimy et al (2012)[47] in which recurrence was higher in males.

PR positivity in non recurrent and recurrent tumours:(TABLE 11)

In the current study, PR positive immunoreactivity was observed in 78% of non recurrent cases and 14% cases of recurrent cases. The results

were analysed using chi-square analysis which is statistically significant.(p=0.03) Our results were similar to results obtained in study by Al-Nuaimy et al (2012) in which PR positivity was observed as 72% and 42% in non-recurrent and recurrent tumours respectively [47].Also a study by Roser et al (2004) showed a higher PR positivity in primary or non recurrent tumours(53.5%)than in recurrent tumours.[46]

Ki 67 status in our current study was 43 % positive (TABLE 12) which is similar to a study by Ashraf Faharjon et al., 2012 , Ki 67 positivity of 38%.[44]

On comparing the Ki 67 positivity among primary and recurrent meningiomas, it was 100% positive in recurrent tumours compared to only 26% of positivity in primary meningiomas. (TABLE 13),which is in accordance with a study by Uranic et al., 2010 and Shalinee Rao et al., 2009, Ki 67 positivity was higher in recurrent tumours[.45] and also the study by El- Badawy et al., 2013 ,where the mean Ki67 positivity was more in recurrant tumours.[43]

In our current study the relationship of Ki 67 positivity and PR status was inversely proportional i.e Ki 67 positivity was present in only 4(21%) PR positive cases with Ki 67 negative in 15(79%) in a total of 19 PR positive cases in our study(table 14). This result correlates well with other studies which are as follows.

In a study byEl- Badawy et al (2013) mean Ki67 positivity in PR negative tumours was 10.31% whereas in PR positive cases, mean Ki67 positivity was only 3.56 [43].Another study by Al-Nuaimy et al (2012) showed mean Ki67 positivity in PR positive cases as 1.6% and 5.8% in PR negative cases[47]. Mauiri et al (2009) showed high Ki67 positivity in PR negative cases were highly predictive of recurrence. [52]

SUMMARY AND CONCLUSION

SUMMARY & CONCLUSION

Meningiomas are categorised into three grades according to WHO classification. In general WHO grade I tumours behave in a benign fashion. [53].However a small subset of tumours appear morphologically benign and biologically aggressive. Detection of these subset of meningiomas is not in routine practice. Thus the study of Progesterone receptor, Estrogen receptor and Ki67 markers were used as an adjuvant approach in the identification of these histologically "on the fence" tumours.[54]

Thirty cases of meningioma were included in the study, all of which were Grade I tumours. Progesterone receptor positivity is seen in about 63.3% of cases, with none of the 30 cases showing immunoreactivity to estrogen receptor.PR expression was higher in females(68%) in comparing with the males. Age, location of tumour and meningioma subtypes had no correlation with PR.[55] The recurrence rate was found to be higher in males (25%). Progesterone expression was higher in Non recurrent tumours (78%). In recurrent tumours, PR expression was decreased (14%) but in contrast Ki67 expression was 100% . There is an inverse relationship between Ki67 and Progesterone receptor expression.[56] This suggests the role of Ki67 in the prediction of recurrence.[57] Age, Location of tumour and the meningioma subtypes

has no role in predicting the recurrence. Although meningiomas express progesterone receptor, it is independant of Estrogen receptor, unlike the other hormone dependant tumours like breast and uterus[58].Expression of Progesterone receptor is associated with lesser recurrence and better prognosis. These observations re emphasize the need to identify morphologically benign , biologically aggressive meningiomas which can be accomplished with the help of immunohistochemistry using Progesterone receptor and Proliferation index. Progeterone receptor can be used along with other histological parameters for prognostication of meningiomas[59,60]

In the grading of meningiomas , histopathological examination alone is not sufficient, ancillary tests with Progesterone receptor and proliferative marker should be included for prognostication of meningiomas.

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ANNEXURE - I

ANNEXURE I-MASTER CHART

S NO	AGE	SEX	IP NO	HPE NO	LOCATION	HPE DIAGNOSIS	GRADE	RECURRENCE	ER	PR	Ki67
1	54	F	16566	863/13	RT FALX	TRANSITIONAL	I	NEG	0	3+	0
2	57	M	16006	908/13	SPENOID RIDGE	TRANSITIONAL	I	NEG	0	3+	1+
3	50	F	34493	1782/13	LT FRONTAL	MENINGOTHELIAL	I	NEG	0	2+	0
4	30	M	41074	2235/13	RT TP	TRANSITIONAL BI	I	NEG	0	3+	1+
5	44	M	44466	2385/13	MCF	MENINGOTHELIAL	I	POS	0	0	1+
6	34	F	42013	2867/13	SPINAL	PSAMMOMATOUS	I	NEG	0	2+	0
7	64	M	47372	2696/13	RT FALX	TRANSITIONAL	I	POS	0	0	2+
8	60	F	44322	2296/13	SPINAL	TRANSITIONAL	I	NEG	0	4+	0
9	37	F	56014	3034/13	RT PO	TRANSITIONAL	I	NEG	0	3+	0
10	32	F	15967	1089/13	SPINAL	FIBROUS	I	POS	0	0	1+
11	40	F	25590	1346/13	MCF	TRANSITIONAL	I	NEG	0	2+	0
12	36	M	3673	244/14	SPINAL	FIBROUS	I	NEG	0	2+	1+
13	70	F		P75/14	SPINAL	PSAMMOMATOUS	I	POS	0	0	1+
14	44	F	1800	361/14	LT FALX	TRANSITIONAL	I	NEG	0	2+	0
15	65	F	75522	364/14	CEREBELLAR	TRANSITIONAL	I	POS	0	0	3+
16	67	F	11524	1049/14	LT FRONTAL	ANGIOMATOUS	I	NEG	0	2+	0
17	45	M	17737	1173/14	LT PARIETAL	TRANSITIONAL	I	NEG	0	2+	0
18	40	F	16122	1217/14	SPINAL	TRANSITIONAL	I	NEG	0	2+	0
19	45	F	25948	1467/14	SPINAL	FIBROUS	I	POS	0	0	1+
20	38	F	24525	1610/14	RT FRONTAL	MENINGOTHELIAL	I	POS	0	0	2+

21	36	F	34162	2417/14	LT FALX	TRANSITIONAL	I	NEG	0	4+	0
22	32	F	41695	2300/14	CEREBELLAR	FIBROUS	I	NEG	0	3+	0
23	39	F	33172	2344/14	SPHENOID	MENINGOTHELIAL	I	NEG	0	0	0
24	41	F	40499	2410/14	LT FALX	MENINGOTHELIAL	I	NEG	0	0	0
25	27	M	4217	2409/14	CP ANGLE	TRANSITIONAL	I	NEG	0	0	0
26	75	M	30523	2482/14	RT PO	TRANSITIONAL	I	NEG	0	0	1+
27	51	F	43037	2576/14	MCF	MENINGOTHELIAL	I	NEG	0	2+	0
28	52	F	42201	2428/14	CP ANGLE	FIBROUS	I	NEG	0	2+	0
29	39	F	55251	2252/14	LT FP	TRANSITIONAL	I	NEG	0	3+	0
30	29	F	45195	536/14	LTPARIETAL	MENINGOTHELIAL	I	NEG	0	2+	0

ANNEXURE - II

ANNEXURE II

PROFORMA

COIMBATORE MEDICAL COLLEGE

DEPARTMENT OF PATHOLOGY

COIMBATORE

Particulars of the patient:

Name : IP/OP NUMBER:

Age: Ward number:

Sex: occupation:

Address:

Presenting complaints:

Headache

Seizures

New neurological deficit

Proptosis

Family history:

Malignancy +/-

Personal history:

Radiation exposure

GENERAL PHYSICAL EXAMINATION:

Built: Febrile :

Nourishment : Pallor:

Conscious : Jaundice:

Weight : Cyanosis:

Pulse rate: Clubbing:

Respiratory rate : Lymphadenopathy:

SYSTEMIC EXAMINATION:

RS: P/A:

CVS: CNS:

CLINICAL DIAGNOSIS:

RADIOLOGICAL FINDINGS:

X RAY:

CT:

MRI:

MICROSCOPIC FINDINGS:

Histopathological diagnosis:

Immunohistochemistry:

FINAL DIAGNOSIS:

ANNEXURE – III

ANNEXURE III

ABBREVIATIONS

ER-ESTROGEN RECEPTOR

PR-PROGESTERONE RECEPTOR

BI-BRAIN INVASION

TP-TEMPERO PARIETAL

PO-POSTERO OCCIPITAL

MCF-MIDDLE CRANIAL FOSSA

FP-FRONTO PARIETAL

CP-CEREBELLO PONTINE ANGLE

RT-RIGHT

LT-LEFT

NEG-NEGATIVE

POS-POSITIVE